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Study No: ARI10018		
Title: An Evaluation of the Bioequivalence of GI198745/dutasteride Soft Gelatin Capsules Compared to GI198745/dutasteride Cross-linked Gelatin Capsules in Healthy Male Volunteers.		
Rationale: In earlier conventional dissolution testing of GI198745 (dutasteride - Dut) soft gelatin capsules, a problem with cross-linking of gelatin was discovered resulting in decreased solubility of the gelatin and a reduced rate of drug release during in vitro testing. This study was performed to compare the bioequivalence of “fresh”, non-cross-linked and cross-linked capsules.		
Phase: I		
Study Period: 09 Jul 1999 – 03 Sep 1999		
Study Design: Randomized, double-blind, two-treatment, two-period, crossover study.		
Centres: 1 center in the US		
Indication: None		
Treatment: Subjects were randomized to receive a single dose of either Dut 0.5 mg fresh non-cross-linked soft gelatin capsules or Dut 0.5 mg cross-linked soft gelatin capsules. Following a 4-week wash out period, subjects then received a single dose of the other treatment.		
Objectives: The primary objective of this study was to demonstrate the bioequivalence of the cross-linked soft gelatin capsule with respect to the fresh, non-cross-linked soft gelatin capsule.		
Statistical Methods: Twenty-four subjects were recruited into the study in order to have at least 20 evaluable subjects at the end of the study. No estimates of intra-subject variability were available to accurately calculate a sample size. However, this sample size was expected to be adequate to demonstrate bioequivalence provided the intra-subject variability was approximately 25%.		
The primary parameters to be compared for the evaluation of bioequivalence were AUC ₂₄ , AUC ₇₂ , AUC _{last} , AUC _{min} , and AUC _{max} . These parameters were log transformed prior to analysis and compared between treatments using analysis of variance (ANOVA) with sequence, subject within sequence, period, and treatment induced in the model. Least squares (LS) means were estimated for the test and reference treatments, and comparisons between treatments were done using these LS means. The difference between the LS means (test-reference), and the 90% confidence interval (CI) about the difference was computed and these values were exponentiated. Equivalence was assumed if the exponentiated 90% CI's fell within a 0.80-1.25 boundary.		
Study Population: Healthy male subjects aged between 18 and 55 years inclusive, with a body mass index between 19 and 29 kg/m ² inclusive.		
Number of Subjects:	Soft Gel Capsules	Cross-linked capsules
Planned N	24	24
Dosed N	24	24
Completed n (%)	24(100)	21(87.5)
Withdrawn n (%)	0	3 (12.5)
Demographics	All subjects	
N (ITT)	24	
Females: Males	0:24	
Mean Age in Years (sd)	34 (10)	

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Mean Weight in Kg (sd)	80.7 (11.4)	
White n (%)	17 (71)	
Pharmacokinetic (PK) Results:		
PK Parameters	Soft Gel Capsules	Cross-linked capsules
AUC ₂₄ (ng.h/mL), mean (SD)	15.68 (9.10)	14.41 (5.36)
AUC ₇₂ (ng.h/mL), mean (SD)	28.80 (20.16)	26.21 (14.07)
AUC _{last} (ng.h/mL), mean (SD)	34.05 (33.67)	29.51 (22.84)
AUC _∞ (ng.h/mL), mean (SD)	46.27 (43.10)	41.03 (29.48)
C _{max} (ng/mL), mean (SD)	1.82 (0.85)	1.66 (0.45)
λ _z (h ⁻¹), mean (SD)	0.03763 (0.05228)	0.05775 (0.09778)
t _{1/2} (h), mean (SD)	43.51 (28.82)	43.94 (32.69)
T _{max} (h), median (min–max)	2.0 (2.0–3.0)	3.0 (1.0–3.0)
Treatment comparisons	Soft Gel Capsules	Cross-linked capsules
AUC ₂₄ (ng.h/mL)		
Geometric least squares (LS) mean	13.20	13.34
95% CI	(11.91, 14.64)	(12.03, 14.79)
Treatment comparison (cross-linked : soft gel)	1.01	
90% CI	(0.90, 1.14)	
AUC ₇₂ (ng.h/mL)		
Geometric least squares (LS) mean	21.32	21.11
95% CI	(18.72, 24.28)	(18.53, 24.03)
Treatment comparison (cross-linked : soft gel)	0.99	
90% CI	(0.85, 1.15)	
AUC _{last} (ng.h/mL)		
Geometric least squares (LS) mean	21.70	22.03
95% CI	(18.45, 25.52)	(18.73, 25.90)
Treatment comparison (cross-linked : soft gel)	1.02	
90% CI	(0.84, 1.23)	
AUC _∞ (ng.h/mL)		
Geometric least squares (LS) mean	29.34	28.94
95% CI	(24.12, 35.69)	(23.79, 35.20)
Treatment comparison (cross-linked : soft gel)	0.99	
90% CI	(0.79, 1.23)	
C _{max} (ng/mL)		
Geometric least squares (LS)	1.62	1.59

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mean		
95% CI	(1.47, 1.79)	(1.45, 1.76)
Treatment comparison (cross-linked : soft gel)	0.98	
90% CI	(0.88, 1.10)	
Safety Results:		
Most Frequent Adverse Events (AEs) Affecting >1 Subject /Group- On Treatment	Soft Gel Capsules	Cross-linked capsules
N (ITT)	24	24
Subjects with AEs, n (%)	3 (12.5)	2 (8)
Individual AEs experienced by one subject only; <5% incidence		
Serious Adverse Events (SAEs) - On Treatment n (%) [considered by the investigator to be related, possibly related, or probably related to study medication]		
	Soft Gel Capsules	Cross-linked capsules
Subjects with Non-fatal SAEs	0	0
Subjects with Fatal SAEs	0	0

Date Updated: 21-Dec-2004

Publications:

No Publications