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Study No.: 002039/103811	
Title: A mono-centre, open, randomized, three-way, twelve-sequence, cross-over study to determine the extent of absorption (absolute bioavailability), rate of absorption and to further characterize distribution and elimination characteristics of a commercial 250 mg and a 500 mg capsule of flucloxacillin each given as a single oral dose vs. one 250 or 500 mg intravenous dose to 24 healthy male and/or female subjects in the fasting state	
Rationale: In this study the characteristics of the absorption process, extent of absorption (absolute bioavailability), distribution and elimination of flucloxacillin capsules (250 mg and 500 mg) were assessed.	
Phase: I	
Study Period: 7. January 2005 to 16. February 2005.	
Study Design: mono-centre, open, randomized, three-way, twelve-sequence, cross-over study	
Centres: 1 centre in Germany.	
Indication: Determination of pharmacokinetics of flucloxacillin, after oral application of 250 mg or 500 mg capsules and intravenous dosing of 250 mg or 500 mg, as well as calculation of the bioavailability parameters from plasma concentration measurements .	
Treatment: 250 mg and 500 mg flucloxacillin each given as a single oral dose vs. one 250 or 500 mg intravenous dose	
Objectives: Primary objective: To study the absolute bioavailability, distribution and elimination parameters of flucloxacillin from two oral formulations of flucloxacillin in healthy male and/or female subjects.	
<p>Statistical Methods: Pharmacokinetics of flucloxacillin: Primary parameters: F, C_{max}, $AUC_{0 \rightarrow last}$, $AUC_{0 \rightarrow \infty}$, t_{max}, $t_{1/2}$. Secondary parameters: k_{el}, Cl_{tot}, Vd_{ss}, Vd_{β} and residual area. Logarithmic transformation for F, C_{max}, $AUC_{0 \rightarrow last}$, $AUC_{0 \rightarrow \infty}$, t_{max}, $t_{1/2}$, k_{el}, Cl_{tot}, Vd_{ss}, and Vd_{β} of flucloxacillin Untransformed data of F and t_{max} of flucloxacillin ANOVA 90% and 95% confidence interval of the geometric mean for each parameter by treatment. Parametric test for F, C_{max}, $AUC_{0 \rightarrow last}$, $AUC_{0 \rightarrow \infty}$ of flucloxacillin after oral administration and for F, C_{max}, $AUC_{0 \rightarrow last}$, $AUC_{0 \rightarrow \infty}$, t_{max}, $t_{1/2}$, k_{el}, Cl_{tot}, Vd_{ss}, Vd_{β} after intravenous infusion (Shapiro-Wilk test for test of normality, Schuirmann's two-sided test procedures for log-transformed data. Nonparametric test for log-transformed data of $t_{1/2}$, and k_{el} after oral administration (due to absence of normal distribution) and for untransformed data of F and t_{max} of flucloxacillin. Comparisons for F, C_{max}, $AUC_{0 \rightarrow last}$, $AUC_{0 \rightarrow \infty}$ of flucloxacillin after oral administration and C_{max}, $AUC_{0 \rightarrow last}$, $AUC_{0 \rightarrow \infty}$, t_{max}, $t_{1/2}$, k_{el}, Cl_{tot}, Vd_{ss}, Vd_{β} after intravenous infusion. Descriptive only: Residual area of flucloxacillin Safety: Descriptive only</p>	
Study Population: Twenty-four (24) healthy volunteers, male and female subjects, Caucasians, age 18 to 45 years; non-smokers, ex-smokers Exclusion criteria: medical history, vital signs, physical examination, laboratory tests (blood and/or urine) with evidence of clinically significant conditions; 12-lead ECG with clinically significant abnormality; acute infection within 2 weeks preceding 1st study drug administration; any medication on a regular basis (exception females: oral contraceptives) and/or tricyclic antidepressants, antacids, histamine H ₂ -receptor antagonists, antibiotics, non steroid anti-inflammatory drugs or anticoagulants within 8 weeks before the 1 st study drug administration and/or no agreement to take any of those drugs including OTC drugs until the end of the follow-up examination; no agreement not to take any medication, including OTC medicine, antacids, or analgesics within 2 weeks before 1 st drug administration until the end of the follow-up examination; special diet or loss of > 5 kg within last month from a weight reduction diet; regular consumption of large quantities of alcohol (> 20g/day) and/or beverages containing methylxanthines e.g. caffeine (> 0.5L/day altogether); no agreement not to consume: - any beverages or foods containing alcohol 48 h prior to 1 st study drug administration until end of the follow-up examination; - any grapefruit products 7 days prior 1 st study drug administration until end of the follow-up examination, - any beverages or foods containing methylxanthines as well as fruit-juices and any foods containing poppy seed 48 h before 1 st drug administration of either study period until last blood sample of the respective study period was collected	
Number of Subjects:	24

Planned, N	24
Entered, N	24
Completed, n (%)	24 (100)
Total Number Subjects Withdrawn, n (%)	0 (0)
Withdrawn due to Adverse Events, n (%)	0(0)
Withdrawn due to Lack of Efficacy, n (%)	not applicable
Withdrawn for Other Reasons, n (%)	0(0)

Demographics	
N (Completed subjects)	24 (100)
Females: Males	11:13
Mean Age, years (range)	26 ± 3 (21 - 30)
Caucasian, n (%)	24 (100)

Primary Results:					
Pharmacokinetics of flucloxacillin (treatment A, 250mg capsule)					
N, total pharmacokinetic population					24
Variable	geom. mean	arithm. mean	std. dev.	range	median
F [%]	54.7	55.4	9.20	42.3 – 71.5	54.0
C _{max} [µg/mL]	7.86	8.33	2.88	3.77 – 15.2	8.08
C _{max, normalized} [µg/mL]	15.7	16.7	5.77	7.55 – 30.3	16.2
AUC _{0→last} [µg·h/mL]	14.7	15.4	4.91	7.89 – 26.8	15.4
AUC _{0→last, normalized} [µg·h/mL]	29.4	30.9	9.83	15.8 – 53.7	30.7
AUC _{0→∞} [µg·h/mL]	14.8	15.5	4.92	7.91 – 26.9	15.4
AUC _{0→∞, normalized} [µg·h/mL]	29.5	31.0	9.84	15.8 – 53.8	30.8
t _{max} [h]	0.92	0.95	0.23	0.75 – 1.50	0.88
t _{1/2} [h]	1.85	1.89	0.42	1.28 – 3.05	1.82
k _{el} [1/h]	0.375	0.382	0.077	0.227 – 0.541	0.382
Residual area [%]	0.3	0.4	0.2	0.2 – 0.7	0.3
Pharmacokinetics of flucloxacillin (treatment B, 500mg capsule)					
N, total pharmacokinetic population					24
Variable	geom. mean	arithm. mean	std. dev.	range	median
F [%]	45.5	48.0	15.5	22.1 – 74.5	47.6
C _{max} [µg/mL]	12.5	13.8	5.97	4.48 – 30.8	13.2
AUC _{0→last} [µg·h/mL]	26.8	28.5	10.3	14.5 – 50.5	26.4
AUC _{0→∞} [µg·h/mL]	26.9	28.6	10.3	14.6 – 50.6	26.5
t _{max} [h]	1.03	1.06	0.30	0.75 – 1.75	1.00
t _{1/2} [h]	2.02	2.06	0.47	1.40 – 3.48	1.99
k _{el} [1/h]	0.344	0.351	0.072	0.199 – 0.496	0.348
Residual area [%]	0.2	0.3	0.1	0.1 – 0.7	0.2
Pharmacokinetics of flucloxacillin (treatment C, 250mg infusion)					
N, total pharmacokinetic population					12
Variable	geom. mean	arithm. mean	std. dev.	range	median
C _{max} [µg/mL]	24.0	24.4	5.21	20.0 – 36.6	22.9
C _{max, normalized} [µg/mL]*	48.0	48.9	10.4	39.9 – 73.2	45.8
AUC _{0→last} [µg·h/mL]	26.3	27.0	6.71	18.7 – 43.3	25.2
AUC _{0→last, normalized} [µg·h/mL]*	52.7	54.0	13.4	37.4 – 86.6	50.5
AUC _{0→∞} [µg·h/mL]	26.4	27.1	6.78	18.7 – 43.6	25.3
AUC _{0→∞, normalized} [µg·h/mL]*	52.8	54.2	13.6	37.5 – 87.3	50.6
t _{max} [h]	0.53	0.53	0.03	0.50 – 0.58	0.52
t _{1/2} [h]	1.88	1.90	0.30	1.52 – 2.61	1.78
k _{el} [1/h]	0.368	0.371	0.053	0.267 – 0.46	0.389
Residual area [%]	0.3	0.3	0.2	0.1 – 0.7	0.2
Cl _{tot} [L/h]	9.47	9.69	2.07	5.73 – 13.3	9.89
Vd _{ss} [L]	12.6	12.7	1.63	9.46 – 14.3	13.3
Vd _β [L]	25.7	26.4	6.44	17.6 – 42.0	27.0
* Dose normalized to 500 mg					
Pharmacokinetics of flucloxacillin (treatment D, 500mg infusion)					
N, total pharmacokinetic population					12
Variable	geom. mean	arithm. mean	std. dev.	range	median
C _{max} [µg/mL]	52.4	53.5	11.3	35.6 – 72.1	51.4

AUC _{0→last} [$\mu\text{g} \cdot \text{h/mL}$]	60.1	61.6	14.1	40.8 – 82.7	61.6
AUC _{0→∞} [$\mu\text{g} \cdot \text{h/mL}$]	60.1	61.7	14.1	40.8 – 82.8	61.6
t _{max} [h]	0.53	0.53	0.03	0.50 – 0.53	0.52
t _{1/2} [h]	2.10	2.12	0.35	1.50 – 2.62	2.13
k _{el} [1/h]	0.3	0.3	0.1	0.3 – 0.5	0.3
Residual area [%]	0.1	0.1	0.1	0.1 – 0.2	0.1
Cl _{tot} [L/h]	8.32	8.54	2.11	6.04 – 12.2	8.14
Vd _{ss} [L]	11.8	12.0	2.39	8.99 – 15.8	12.6
Vd _β [L]	25.1	25.7	5.58	16.8 – 35.3	24.6

Secondary Outcome Variable(s): Not applicable.

Safety Results: (Safety Population) – On-therapy adverse events (AEs) and serious adverse events (SAEs) were defined as starting any time after the first dose until the end of the observational period.

	A N=24	B N=24	C N=12	D N=12
Most frequent Adverse Events - On Therapy	n (%)	n (%)	n (%)	n (%)
Subjects with any AE(s), n (%)	11 (46)	8 (33)	4(33)	5 (42)
headache	7 (29)	5 (21)	3 (24)	2(17)
rhinitis	2 (8)	0 (0)	0	0
tiredness	2 (8)	0	0	0
cough	0	2 (8)	0	0
pain during infusion (around the cannula)	0	0	0	2 (17)
Serious Adverse Events (SAEs) - On-Therapy				
n (%) [n considered by the investigator to be related to study medication]				
	Flucloxacillin			
	all groups (N=24)			
	n (%) [related]			
Subjects with non-fatal and fatal SAEs, n (%)	0			

Publications:

No publication

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