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Study No.: 234		
Title: A Comparison of the Efficacy and Safety of Augmentin 875/125 mg po q 12 hours versus Augmentin 500/125 mg po q 8 hours in the Treatment of Lower Respiratory Tract Infections.		
Rationale: In some countries, at the time of this study, amoxicillin/clavulanate was dosed at 500/125 mg orally (po) every (q) 8 hours (three times a day; q 8 hours) for the treatment of community acquired pneumonia (CAP) and acute exacerbation of chronic bronchitis (AECB). The aim of this study was to determine if administration of amoxicillin/clavulanate 875/125 mg po every 12 hours (two times a day; q 12 hours) was no more than 10% better or worse than amoxicillin/clavulanate 500/125 mg po every 8 hours for the treatment of these infections. Pharmacokinetic, microbiological, <i>in vivo</i> animal and clinical data supported the proposed change in regimen.		
Phase: III		
Study Period: 25 September 1992 to 7 June 1993.		
Study Design: A randomized, double-blind, double-dummy, parallel group, multicenter, comparative study. Subjects visited the clinic at screening (days -2 to 0), on-therapy (48-96 hours), end of therapy (EOT) (3±1 days post-therapy) and at follow-up (2 to 4 weeks post-therapy). Clinical status was assessed by a telephone call after 7±2 days on therapy, and there was the possibility of an optional interim visit prior to stopping study medication if clinically indicated.		
Centers: A total of 87 centers in: Australia (1), Belgium (7), Canada (6), Germany (13), Italy (3), the Netherlands (13), Republic of Ireland (8), South Africa (3), Switzerland (2), United Kingdom (15) and United States (16).		
Indication: Lower respiratory tract infection (LRTI), specifically CAP and AECB.		
Treatment: Subjects were randomized in a 1:1 ratio to receive one of two treatments for 7 to 14 days: Amoxicillin/clavulanate 875/125 mg tablets po every 12 hours plus placebo amoxicillin/clavulanate 500/125 mg tablets po every 8 hours or amoxicillin/clavulanate 500/125 mg tablets po every 8 hours plus placebo amoxicillin/clavulanate 875/125 mg tablets po every 12 hours.		
Objectives: The objective was to compare the efficacy and safety of amoxicillin/clavulanate 875/125 mg po every 12 hours and amoxicillin/clavulanate 500/125 mg po every 8 hours in the treatment of subjects with LRTI, specifically CAP and AECB.		
Primary Outcome/Efficacy Variable: Clinical response (success or failure) to study medication at EOT. Clinical success at EOT was defined as sufficient resolution of CAP/AECB such that no additional antibacterial therapy for CAP/AECB was indicated. Clinical failure was recorded when there was insufficient improvement of CAP/AECB at EOT requiring additional antibacterial therapy.		
Secondary Outcome/Efficacy Variable(s): Bacteriological response (success or failure) to study medication at EOT. Bacteriological success was defined as the eradication or, in the absence of an evaluable repeat culture sample, clinical evidence of eradication of all initial screening pathogens without superinfection or new infection. Bacteriological failure was defined as the persistence or recurrence of an initial screening pathogen, or the presence of a new pathogen in a repeat culture sample. For patients with no repeat culture sample available, bacteriological failure was presumed if clinical signs and symptoms persisted to a degree that necessitated further antibacterial therapy for the indication under investigation. If a patient was deemed to be a bacteriological failure at any stage, this outcome was carried forward to all further visits		
Statistical Methods: The safety population included all randomized patients. The clinical per protocol (PP) population included subjects with a clinical diagnosis of CAP or AECB (according to pre-defined criteria), without any violations as specified in the protocol. The bacteriological PP population included those subjects from the clinical PP population that had a pre-therapy organism meeting pre-defined criteria identified at screening. The equivalence of the two treatment groups was also assessed by computing the two-tailed 95% CIs for the difference (every 12 hours minus every 8 hours) in the proportions of subjects with clinical successes. The normal approximation to the binomial distribution was used in constructing the confidence interval. The treatment groups were considered equally effective if the lower 95% confidence limit did not exceed 10%. It should be noted that the study was not designed to demonstrate equivalence for secondary end-points where the numbers of patients was too small to draw any conclusions.		
Study Population: Male and female subjects, aged 18 years and older, with either CAP or AECB, as defined by signs and symptoms as given in the protocol. Patients with concomitant infection or onset of symptoms more than 72 hours after hospital admission (CAP only) were excluded.		
	Amoxicillin/clavulanate	Amoxicillin/clavulanate

	500/125mg q 8 hours	875/125mg q 12 hours
Number of Subjects:		
Planned, N (evaluable)	150	150
Randomized, N	284	273
Clinical PP Population at EOT, N	228	227
Bacteriological PP Population at EOT, N	63	59
Completed, n (%)	240 (84.5)	232 (85.0)
Total Number Subjects Withdrawn, n (%)	44 (15.5)	41 (15.0)
Withdrawn due to Adverse Events, n (%)	22 (7.7)	16 (5.9)
Withdrawn due to Lack of Efficacy, n (%)	5 (1.8)	5 (1.8)
Withdrawn for Other Reasons, n (%)	17 (6.0)	20 (7.3)
Demographics	Amoxicillin/clavulanate 500/125mg q 8 hours	Amoxicillin/clavulanate 875/125mg q 12 hours
N (Safety Population)	284	273
Females: Males	107: 177	104: 169
Mean Age, years (SD)	57.5 (17.3)	56.3 (18.4)
White, n (%)	265 (93.3)	239 (87.5)
Primary Efficacy Results: (Clinical PP Population)		
Clinical response at EOT:	Amoxicillin/clavulanate 500/125mg q 8 hours (N=228)	Amoxicillin/clavulanate 875/125mg q 12 hours (N=227)
Clinical response for all infections, N (evaluable)	228	227
Success, n (%)	215 (94.3)	212 (93.4)
Failure, n (%)	13 (5.7)	15 (6.6)
Treatment Difference 95% CI	-5.3, 3.5	
p-value	0.424	
Clinical response for CAP, N (evaluable)	117	120
Success, n (%)	112 (95.7)	113 (94.2)
Failure, n (%)	5 (4.3)	7 (5.8)
Treatment Difference 95% CI	-7.1, 4.0	
p-value	Not available	
Clinical response for AECB, N (evaluable)	111	107
Success, n (%)	103 (92.8)	99 (92.5)
Failure, n (%)	8 (7.2)	8 (7.5)
Treatment Difference 95% CI	-7.2, 6.7	
p-value	Not available	
Secondary Outcome Variable(s): (Bacteriological PP Population)		
	Amoxicillin/clavulanate 500/125mg q 8 hours (N=63)	Amoxicillin/clavulanate 875/125mg q 12 hours (N=59)
Bacteriological response at EOT:		
Bacteriological response for all infections, N (evaluable)	63	59
Success, n (%)	57 (90.5)	57 (96.6)
Failure, n (%)	6(9.5)	2 (3.4)
Treatment Difference 95% CI	-2.5, 14.7	
Bacteriological response for CAP, N (evaluable)	29	35
Success, n (%)	28 (96.6)	34 (97.1)
Failure, n (%)	1 (3.4)	1 (2.9)
Treatment Difference 95% CI	-8.0, 9.2	
Bacteriological response for AECB, N (evaluable)	34	24
Success, n (%)	29 (85.3)	23 (95.8)
Failure, n (%)	5 (14.7)	1 (4.2)
Treatment Difference 95% CI	-3.8, 24.9	
Safety Results: Safety Population – Adverse events (AEs) and serious AE (SAE) were reported that occurred during the study from the point of randomization until follow-up. AEs reported on-therapy and up to 30 days post-therapy		

were summarized.		
	Amoxicillin/clavulanate 500/125mg q 8 hours (N=284)	Amoxicillin/clavulanate 875/125mg q 12 hours (N=273)
Most Frequent Adverse Events – On-Therapy plus 30 Days Post-Therapy	n (%)	n (%)
Subjects with any AE(s), n (%)	106 (37.3)	116 (42.5)
Diarrhea	35 (12.3)	30 (11.0)
Nausea	13 (4.6)	16 (5.9)
Headache	13 (4.6)	14 (5.1)
Abdominal pain	8 (2.8)	12 (4.4)
Vomiting	8 (2.8)	7 (2.6)
Asthma	5 (1.8)	5 (1.8)
Rash	4 (1.4)	5 (1.8)
Moniliasis genital	5 (1.8)	4 (1.5)
Respiratory disorder	5 (1.8)	3 (1.1)
Dyspepsia	4 (1.4)	1 (0.4)
Moniliasis	4 (1.4)	3 (1.1)
Chest pain	2 (0.7)	4 (1.5)
Sinusitis	1 (0.4)	4 (1.5)
Serious Adverse Events - On-Therapy plus 30 Days Post-Therapy n (%) [n considered by the investigator to be related to study medication]		
	Amoxicillin/clavulanate 500/125mg q 8 hours (N=284)	Amoxicillin/clavulanate 875/125mg q 12 hours (N=273)
Subjects with fatal or non-fatal SAEs, n (%)	12 (4.2)	8 (2.9)
	n (%) [related]	n (%) [related]
Injury	1 (0.4) [0]	2 (0.7) [0]
Abdominal pain	0	2 (0.7) [0]
Cardiac failure	1 (0.4) [0]	1 (0.4) [0]
Neoplasm, not otherwise specified	1 (0.4) [0]	1 (0.4) [0]
Angina pectoris	0	1 (0.4) [0]
Arthritis	0	1 (0.4) [0]
Cholelithiasis	0	1 (0.4) [0]
Fever	0	1 (0.4) [0]
Fibrillation ventricular	0	1 (0.4) [0]
Myalgia	0	1 (0.4) [0]
Myocardial infarction	0	1 (0.4) [0]
Nausea	0	1 (0.4) [0]
Respiratory disorder	2 (0.7) [2]	0
Dyspnea	2 (0.7) [0]	0
Anorexia	1 (0.4) [0]	0
Anuria	1 (0.4) [0]	0
Asthma	1 (0.4) [0]	0
Bradycardia	1 (0.4) [0]	0
Confusion	1 (0.4) [0]	0
Coughing	1 (0.4) [0]	0
Fibrillation atrial	1 (0.4) [0]	0
Infection bacterial	1 (0.4) [1]	0
Pneumonia	1 (0.4) [0]	0
Respiratory insufficiency	1 (0.4) [0]	0
Sepsis	1 (0.4) [1]	0
Tachycardia	1 (0.4) [0]	0
Subjects with fatal SAEs, n (%)	2 (0.7)	1 (0.4)
	n (%) [related]	n (%) [related]

Cardiac arrest	1 (0.4) [0]	0
Cerebrovascular disorder	0	1 (0.4) [0]
Pneumonia	0	1 (0.4) [0]
Pulmonary carcinoma	1 (0.4) [0]	0

Conclusion:

See publication below.

Publications:

Calver A, Walsh N, Quinn P, Baran C, Lonergan V, Singh K, Orzolek W, et al. Dosing of Amoxicillin/Clavulanate Given Every 12 Hours Is as Effective as Dosing Every 8 Hours for Treatment of Lower Respiratory Tract Infection. *Clinical Infectious Disease* 1997; 24:570-4

Augmentin BID versus Augmentin TID in the Treatment of Lower Respiratory Tract Infections (LRTI), Calver, A D, MD; Walsh, N, MD; Quinn, P, MD. Orkney, South Africa; Longford, Ireland; Sligo, Ireland; Montreal, QC; Canada. 19th International Congress of Chemotherapy. 7/16/1995

Amoxicillin/Clavulanate BID vs. A/C TID in the Treatment of Lower Respiratory Tract Infections, Calver, A, MD; Walsh, N, MD; Quinn, P, MD. Orkney, South Africa; Longford, Ireland; Sligo, Ireland; San Francisco, CA; USA. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). 9/17/1995

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