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Study No.: 551
Title: An Open, Non-Comparative Multicenter Study to Assess the Efficacy and Safety of Oral <i>AUGMENTIN SR</i> 2000/125mg Twice Daily for 10 Days in the Treatment of Acute Bacterial Sinusitis in Adults.
Rationale: The purpose of this study was to examine the clinical and bacteriological efficacy and safety of oral Augmentin SR tablets (pharmacokinetically enhanced amoxicillin/clavulanate), 2000/125mg twice daily (bid) for 10 days for the treatment of subjects with acute bacterial sinusitis (ABS), in particular, in those with infection due to penicillin-resistant <i>Streptococcus pneumoniae</i> (PRSP).
Phase: III
Study Period: 15 November 1999 to 29 June 2000.
Study Design: Open-label, non-comparative, multicenter study. Subjects were instructed to attend the clinic at screening (Visit 1, day 1), on-therapy (Visit 2, day 3-5), end of therapy (Visit 3, day 12-14) and follow up (Visit 4, day 17-24). (For purposes of analysis, the number of days allowed for the visits were expanded as follows: Visit 1 : Days -2 to 1; Visit 3 : Days 11-16; Visit 4 : Days 17-28.)
Centers: The study was conducted at 83 centers in four countries: Czech Republic (4), Hungary (10), Poland (12) and the United States (57).
Indication: Acute bacterial sinusitis.
Treatment: Subjects received 10 days of treatment with amoxicillin/clavulanate SR 2000/125mg bid.
Objectives: The primary objective was to assess the bacteriological efficacy at the follow up visit, of oral amoxicillin/clavulanate SR 2000/125mg bid for 10 days in subjects with ABS, in particular, infection due to PRSP. The secondary objectives were: 1) to assess the bacteriological and clinical efficacy at the end of therapy visit of oral amoxicillin/clavulanate SR 2000/125mg bid for 10 days in subjects with ABS, in particular, infection due to PRSP, 2) to evaluate the clinical efficacy at the follow up visit of oral amoxicillin/clavulanate SR 2000/125mg bid for 10 days in subjects with ABS, and 3) to assess the safety of oral amoxicillin/clavulanate SR 2000/125mg bid for 10 days in subjects with ABS, 4) to assess the incidence of adverse experiences (AEs) in adult subjects receiving amoxicillin/clavulanate SR 2000/125mg bid for 10 days in the treatment of ABS.
Primary Outcome/Efficacy Variable: The bacteriological response (success or failure) at follow-up (Visit 4). 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 subjects 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 subject was deemed to be a bacteriological failure at any stage, this outcome was carried forward to all further visits.
Secondary Outcome/Efficacy Variable(s): Bacteriological response (success or failure) at the end of therapy (Visit 3). 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 subjects 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 subject was deemed to be a bacteriological failure at any stage, this outcome was carried forward to all further visits. Clinical response (success or failure) at follow-up (Visit 4). Clinical response (success or failure) at end of therapy (Visit 3). Clinical success was defined as sufficient resolution of ABS such that no additional antibacterial therapy for ABS was indicated. Clinical failure was recorded when there was insufficient improvement of ABS at end of therapy requiring additional antibacterial therapy. Clinical failure at follow up was defined as reappearance or deterioration of ABS following clinical success at end of therapy. If a subject was deemed to be a clinical failure at any stage, this outcome was carried forward to all further visits. Combined clinical and radiological response (success, failure or unable to determine) at follow-up (Visit 4). Clinical success was defined as sufficient resolution of ABS such that no additional antibacterial therapy for ABS was

<p>indicated. Clinical failure at follow up was defined as reappearance or deterioration of ABS following clinical success at end of therapy. If a subject was deemed to be a clinical failure at any stage, this outcome was carried forward to all further visits. Radiological outcome of improved was defined as improvement or resolution of radiological signs of ABS. Radiological outcome of unchanged was defined as no improvement in the baseline radiological signs of ABS. Radiological outcome of worse was defined as a worsening of the baseline radiological signs of ABS, or the appearance of new radiological signs of ABS. Unable to determine was defined as a valid assessment if radiological outcome could not be made.</p> <p>Combined clinical and radiological response at follow up was defined as: Success if clinical success and radiological outcome of improved or unchanged; Failure if clinical failure at end of therapy, or clinical outcome at follow up was recurrence, and/or radiological outcome of worse at follow up; Unable to determine if either the subject's clinical outcome at end of therapy or follow up was unable to determine and radiological outcome at follow up was improved, unchanged, unable to determine, or unknown; or the clinical response at follow up was success and the radiological outcome was unable to determine or unknown.</p>		
<p>Statistical Methods: The intent-to-treat (ITT) population included all subjects who took at least one dose of study medication; the bacteriology ITT population included all subjects who took at least one dose of study medication and had at least one pre-therapy pathogen identified at screening. The safety population was the same as the ITT population. The primary efficacy analysis variable was the per subject bacteriological response at follow up and the principal efficacy analysis was an estimate of the proportion of successes for the bacteriology ITT population. For all efficacy analyses, a two-sided 95% confidence interval (CI) for the estimates of the proportion of successes was presented incorporating a continuity correction of a half.</p>		
<p>Study Population: Male or female subjects ≥ 16 years of age, with radiologically-confirmed ABS. Subjects had respiratory signs and symptoms of ABS for at least 3 days (for severe cases) to 7 days (for mild or moderate cases) but less than 28 days duration, as defined by purulent nasal discharge or purulence in the nasal cavity on examination and at least one major or two minor criteria:</p> <p>Major criteria: facial pain/pressure/tightness over affected sinus(es), facial congestion/fullness, or nasal obstruction/blockage.</p> <p>Minor criteria: tooth pain, earache, non-vascular headache, sore throat, cough, halitosis, fever, change in perception of smell, or periorbital swelling.</p> <p>Subjects with a history of chronic sinusitis, intraorbital or intracranial complications that would have interfered with the interpretation of the radiological images, prior sinus surgery, concomitant infection, or treatment with antibiotics within seven days were excluded.</p>		
	Amoxicillin / clavulanate SR 2000 / 125mg bid	
Number of Subjects:	Efficacy Population*	Safety Population*
Planned, N	600	
Entered, N	781	806
Treated (ITT population), N	779	804
Bacteriology ITT population, N	334	370
Completed, n (% of ITT population)	729 (93.6)	754 (93.8)
* 861 subjects were enrolled; all 55 subjects from one US center were excluded from the efficacy and safety populations at the request of the Food and Drug Administration (FDA) and all 25 subjects from another US center were excluded from the efficacy population because of incorrect sample collection procedures.		
Total Number Subjects Withdrawn, n (% of Efficacy ITT population)	50 (6.4)	
Withdrawn due to Adverse Events, n (%)	13 (1.7)	
Withdrawn due to Lack of Efficacy, n (%)	0	
Withdrawn for Other Reasons, n (%)	37 (5.1)	
	Amoxicillin / clavulanate SR 2000 / 125mg bid	
N (Efficacy ITT)	779	
Females: Males	447:332	
Mean Age, years (SD)	40.8 (13.6)	
White, n (%)	695 (89.2)	
Primary Efficacy Results: Bacteriology ITT Population		
	Amoxicillin / clavulanate SR 2000 / 125mg bid (N=334)	

Bacteriological Response at Follow Up	
Success, n (%)	290 (86.8)
Failure, n (%)	44 (13.2)
95% CI for Success Rate	82.6, 90.2
p-value	Not available
Secondary Outcome Variable(s):	
	Amoxicillin / clavulanate SR 2000 / 125mg bid
Bacteriological Response at End of Therapy: Bacteriology ITT Population	N=334
Success, n (%)	311 (93.1)
Failure, n (%)	23 (6.9)
95% CI for Success Rate	89.7, 95.5
Clinical Response at Follow Up: Efficacy ITT Population	N=779
Success, n (%)	682 (87.5)
Failure, n (%)	97 (12.5)
95% CI for Success Rate	85.0, 89.7
Clinical Response at End of Therapy: Efficacy ITT Population	N=779
Success, n (%)	730 (93.7)
Failure, n (%)	49 (6.3)
95% CI for Success Rate	91.7, 95.3
Combined Clinical and Radiological Response at Follow Up: Efficacy ITT Population	N=779
Success, n (%)	657 (84.3)
Failure, n (%)	70 (9.0)
Unable to Determine, n (%)	52 (6.7)
95% CI for Success Rate	81.6, 86.8
Safety Results: AEs were summarized that occurred on-therapy and up to and including 30 days after the last day of study medication.	
	Amoxicillin / clavulanate SR 2000 / 125mg bid (N=804)
Most Frequent Adverse Events – On-Therapy Plus 30 Days Post-Therapy	n (%)
Subjects with any AE(s), n (%)	313 (38.9)
Diarrhea	133 (16.5)
Injury	24 (3.0)
Nausea	22 (2.7)
Abdominal pain	19 (2.4)
Genital moniliasis	19 (2.4)
Headache	17 (2.1)
Flatulence	15 (1.9)
Gastrointestinal disorder, not otherwise specified	15 (1.9)
Rash	12 (1.5)
Epistaxis	10 (1.2)
Fungal infection	10 (1.2)
Vaginitis	10 (1.2)
Serious Adverse Events (SAEs) - On-Therapy Plus 30 Days Post-Therapy n (%) [n considered by the investigator to be related to study medication]	
	Amoxicillin / clavulanate SR 2000 / 125mg bid (N=804)
	n (%) [related]
Subjects with non-fatal SAEs, n (%)	2 (0.2) [0]
Epistaxis	1 (0.1) [0]
Angina pectoris	1 (0.1) [0]

	n (%) [related]
Subjects with fatal SAEs, n (%)	0

Conclusion:

See publication below.

Publications:

Garau J, Jacobs MR, Wynne B, Berkowitz E, Twynholm M. Pharmacokinetically enhanced amoxicillin/clavulanate (AMX/CA) 2000/125 mg in the treatment of community-acquired pneumonia (CAP) and acute bacterial sinusitis (ABS) caused by *Streptococcus pneumoniae*. Abstracts from the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, USA. September 2003, page 422, Abstract L-1382.

File T, Jacobs MR, Poole MD, Wynne B. Outcome of treatment of respiratory tract infections due to *Streptococcus pneumoniae*, including drug-resistant strains, with pharmacokinetically enhanced amoxicillin/clavulanate. *Int J Antimicrob Agents* 2002; 20(4): 235–47.

Poole MT, Ferguson B, Klossek J-M, Anon JB, Jacobs MR. Efficacy and safety of pharmacokinetically enhanced amoxicillin/clavulanate twice daily for 10 days in the treatment of acute bacterial sinusitis in adults. Abstracts from the 2nd Forum on Respiratory Tract Infections, Monte Carlo, Monaco. February 2002, page 85, Abstract P16 (note: data since revised)

Poole MD, Ferguson BJ, Klossek J-M, Anon J, Jacobs MR, Baxendale S, Richard M, Wynne B, The 551 Study Group. Clinical efficacy and safety of pharmacokinetically enhanced amoxicillin/clavulanate (AMX/CA) b.d. for 10 days in the treatment of acute bacterial sinusitis (ABS) in adults. Abstracts from the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, USA. September 2001, page 461, Abstract L-911 (note: data since revised)

Garau J, File T, Jacobs MR, Poole MD, Wynne B, The 546–551, 566, 557 and 592 Clinical Study Groups. Efficacy of amoxicillin/clavulanate (AMX/CA) 2000/125 mg b.i.d. against *Streptococcus pneumoniae* non-susceptible to AMX. Abstracts from the 4th International Meeting on the Therapy of Infections, Florence, Italy. October 2002, page 71, Abstract A5

File T, Jacobs MR, Poole MD, Wynne B. Pharmacokinetically enhanced amoxicillin/clavulanate against *Streptococcus pneumoniae* (Sp) in respiratory tract infections (RTIs). Abstracts from the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, USA. September 2002, page 359, Abstract L-990

File T, Jacobs MR, Poole MD, Wynne B. Clinical efficacy of pharmacokinetically enhanced amoxicillin/clavulanate (AMX/CA) vs comparators against *Streptococcus pneumoniae* (Sp) in respiratory tract infections (RTIs). Abstracts from the 2nd Forum on Respiratory Tract Infections, Monte Carlo, Monaco. February 2002, page 62, Abstract P4

Garau J, Jacobs MR, Wynne B, Berkowitz E, Twynholm M. Pharmacokinetically enhanced amoxicillin/clavulanate (AMX/CA) 2000/125 mg in the treatment of community-acquired pneumonia (CAP) and acute bacterial sinusitis (ABS) caused by *Streptococcus pneumoniae*. Abstracts from the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, USA. September 2003, page 422, Abstract L-1382.

Efficacy and Safety of Pharmacokinetically Enhanced Amoxicillin/Clavulanate 2000/125 mg (PKE AMX/CA) in Adult Patients with Acute Bacterial Sinusitis (ABS), JACK B. ANON, MDI, ELCHONON BERKOWITZ, PhD2, JOHN BRETON, MCM2@ MONIQUE TWYNHOLM, MSC3. IUniv of Pittsburgh College of Medicine, Erie, PA,2GlaxoSmithKline, Collegeville, PA,3GlaxoSmithKline, Greenford, United Kingdom.; Boston, MA; USA. 42nd Annual Meeting of the Infectious Diseases Society of America. 9/30/2004

Efficacy and safety of pharmacokinetically enhanced amoxicillin/clavulanate 2000/125 mg in adult patients with acute bacterial sinusitis in Hungary, Tamas, L.; Kovacs, P.; Horvai, G.; Twynholm, M. Budapest, HUN; Harlow, UK; Prague; Czech Republic. 14th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID). 5/1/2004

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