

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

<b>Study No.:</b> 549
<b>Title:</b> A Randomised, Double-blind, Double-dummy, Multicentre, Parallel Group Study to Assess the Efficacy and Safety of Oral Augmentin SR 2000/125mg Twice Daily for 7 days versus Oral Levofloxacin 500mg Once a Day for 7 Days in the Treatment of Acute Exacerbation of Chronic Bronchitis.
<b>Rationale:</b> The aim of this study was to evaluate whether amoxicillin/clavulanate (SR) 2000/125mg twice daily (bid) for 7 days was at least as clinically and bacteriologically effective as levofloxacin 500mg once daily (od) for 7 days, in the treatment of subjects with acute exacerbation of chronic bronchitis (AECB).
<b>Phase:</b> III
<b>Study Period:</b> 8 November 1999 to 17 February 2000.
<b>Study Design:</b> Randomised, double-blind, multicentre, double-dummy, parallel group study. Subjects made five clinic visits: screening (Visit 1, Days-2 to 0), on-therapy (Visit 2, Days 3 to 5), end of therapy (EOT), (Visit 3, Days 8 to 13), follow-up, (FU) (Visit 4, Days 14 to 23) and long term follow-up (LTFU), (Visit 5, Days 25 to 38)
<b>Centres:</b> The study was conducted at 92 centres in 6 countries: Belgium (7), France (22), Germany (20), Ireland (8), United Kingdom (11), and United States (24).
<b>Indication:</b> Acute exacerbation of chronic bronchitis.
<b>Treatment:</b> Subjects were randomized on a 1:1 basis to receive either oral amoxicillin/clavulanate SR 2000/125mg bid and oral levofloxacin placebo od for 7 days or oral levofloxacin 500mg od and oral amoxicillin/clavulanate SR placebo bid for 7 days.
<b>Objectives:</b> The primary objective was to demonstrate that oral amoxicillin/clavulanate SR 2000/125mg bid for 7 days was at least as effective clinically as oral levofloxacin 500mg od for 7 days for the treatment of AECB
<b>Primary Outcome/Efficacy Variable:</b> The clinical response (success or failure) at FU (Visit 4). Clinical success was defined as sufficient resolution of AECB such that no additional antibacterial therapy for AECB was indicated. Clinical failure was recorded when there was insufficient improvement of AECB at EOT requiring additional antibacterial therapy. Clinical failure at FU and LTFU was defined as reappearance or deterioration of AECB following clinical success at previous visits. If a subject was deemed to be a clinical failure at any stage, this outcome was carried forward to all further visits.
<b>Secondary Outcome/Efficacy Variable(s):</b> Clinical response (success or failure) at EOT (Visit 3). Clinical response (success or failure) at LTFU (Visit 5). Bacteriological response (success or failure) at FU (Visit 4). Bacteriological response (success or failure) at EOT (Visit 3). Bacteriological response (success or failure) at LTFU (Visit 5). Therapeutic response (success or failure) at FU. Therapeutic response (success or failure) at EOT. Therapeutic response (success or failure) at LTFU. 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. Therapeutic response was based on combined clinical and bacteriological response.
<b>Statistical Methods:</b> The safety population included all randomised subjects who took at least one dose of study medication. The clinical per-protocol (PP) population was a subset of the safety population that excluded subjects who violated any aspect of the protocol to an extent that may affect treatment efficacy. The bacteriology PP population included all randomised subjects who took at least one dose of study medication and had at least one pre-therapy pathogen identified at screening and excluded subjects who violated any aspect of the protocol to an extent that may affect treatment efficacy. The primary efficacy analysis was based on an unstratified comparison of clinical response proportions between the treatment groups in the clinical PP population. Two-sided 95% confidence intervals (CIs) were used to estimate the difference in the proportion of successes between the treatment groups. A conclusion of non-inferior efficacy of amoxicillin/clavulanate SR was drawn if the lower limit of the CI (amoxicillin/clavulanate SR

minus levofloxacin) was  $\geq 10\%$ . All CIs for differences in proportions were calculated using the normal approximation to the binomial distribution.

It should be noted that the study was not designed to demonstrate non-inferiority for secondary end-points where the numbers of subjects was too small to draw any conclusions.

**Study Population:** Subjects of either gender, at least 40 years of age, with a history of chronic bronchitis characterised by cough and sputum production for more than two consecutive years and for most days in a consecutive three-month period in each year. Subjects were to have AECB characterised by increased purulent sputum together with increased cough and increased dyspnoea and be suitable for oral therapy. Subjects were excluded if they had a known hypersensitivity to study drugs, known or suspected renal or liver function impairment, were immunocompromised, HIV positive with a CD4 count  $< 200\text{mm}^3$  or had any complicating disease or infection that would complicate evaluation of study treatment, including pneumonia (clinically and radiologically confirmed), cystic fibrosis, active tuberculosis, bronchiectasis and active pulmonary malignancy, a history of tendonitis whilst on quinolone therapy, history of epilepsy, convulsions or myasthenia gravis, clinical history of haemolytic crisis or glucose-6-phosphate dehydrogenase (G6PD) deficiency. The use of prohibited medications including systemic corticosteroids ( $>10$  mg/day prednisone or equivalent), antacids containing aluminum or magnesium salts, vitamins and minerals containing iron and renal tubular secretion inhibitors such as probenecid was also a basis for exclusion, as was the use of any systemic antibacterial within 7 days prior to study entry.

	<b>Amoxicillin / clavulanate SR 2000 / 125mg bid</b>	<b>Levofloxacin 500mg od</b>
Number of Subjects:		
Planned, N	300	300
Randomised, N	308	316
Safety Population, N	307	315
Completed, n (% of Safety Population)	274 (89.3)	281 (89.2)
Clinical PP Population at FU, N	255	264
Bacteriological PP Population at FU, N	65	59
Total Number Subjects Withdrawn, n (%)	33 (10.7)	34 (10.8)
Withdrawn due to Adverse Events, n (%)	15 (4.9)	17 (5.4)
Withdrawn due to Lack of Efficacy, n (%)	3 (1.0)	1 (0.3)
Withdrawn for Other Reasons, n (%)	15 (4.9)	16 (5.1)
<b>Demographics</b>	<b>Amoxicillin / clavulanate SR 2000 / 125mg bid</b>	<b>Levofloxacin 500mg od</b>
N (Safety Population)	307	315
Females: Males	126: 181	141: 174
Mean Age, years (SD)	62.7 (11.6)	61.5 (11.7)
White, n (%)	298 (97.1)	306 (97.1)
<b>Primary Efficacy Results: Clinical PP Population</b>		
	<b>Amoxicillin / clavulanate SR 2000 / 125mg bid (N=255)</b>	<b>Levofloxacin 500mg od (N=264)</b>
Clinical Response at FU		
Success, n (%)	219 (85.9)	230 (87.1)
Failure, n (%)	36 (14.1)	34 (12.9)
Treatment Difference % (Amox/clav SR – Levoflox)	-1.2	
95% CI	-7.1, 4.6	
p-value	Not applicable	
<b>Secondary Outcome Variable(s):</b>		
	<b>Amoxicillin / clavulanate SR 2000 / 125mg bid</b>	<b>Levofloxacin 500mg od</b>
Clinical Response at EOT: Clinical PP Population		
	N=258	N=270
Success, n (%)	244 (94.6)	252 (93.3)
Failure, n (%)	14 (5.4)	18 (6.7)
Treatment Difference % (Amox/clav SR – Levoflox)	1.2	
95% CI	-2.8, 5.3	
Clinical Response at LTFU: Clinical PP Population		

	N=244	N=258
Success, n (%)	205 (84.0)	211 (81.8)
Failure, n (%)	39 (16.0)	47 (18.2)
Treatment Difference % (Amox/clav SR – Levoflox)	2.2	
95% CI	-4.3, 8.8	
Bacteriological Response at FU: Bacteriological PP Population		
	N=65	N=59
Success n (%)	52 (80.0)	49 (83.1)
Failure n (%)	13 (20.0)	10 (16.9)
Treatment Difference % (Amox/clav SR – Levoflox)	-3.1	
95% CI	-16.7, 10.6	
Bacteriological Response at EOT: Bacteriological PP Population		
	N=67	N=66
Success, n (%)	64 (95.5)	59 (89.4)
Failure, n (%)	3 (4.5)	7 (10.6)
Treatment Difference % (Amox/clav SR – Levoflox)	6.1	
95% CI	-2.8, 15.1	
Bacteriological Response at LTFU: Bacteriological PP Population		
	N=63	N=58
Success, n (%)	44 (69.8)	43 (74.1)
Failure, n (%)	19 (30.2)	15 (25.9)
Treatment Difference % (Amox/clav SR – Levoflox)	-4.3	
95% CI	-20.3, 11.7	
Therapeutic Response at FU : Bacteriology PP Population		
	N= 65	N=59
Success, n (%)	52 (80.0)	49 (83.1)
Failure, n (%)	13 (20.0)	10 (16.9)
Therapeutic Response at EOT : Bacteriology PP Population		
	N= 67	N=66
Success, n (%)	63 (94.0)	55 (83.3)
Failure, n (%)	4 (6.0)	11 (16.7)
Therapeutic Response at LTFU : Bacteriology PP Population		
	N= 63	N=58
Success, n (%)	43 (68.3)	43 (74.1)
Failure, n (%)	20 (31.7)	15 (25.9)
<b>Safety Results: Safety Population</b> - An adverse event (AE) occurring during the interval on therapy and within 30 days post therapy was defined as an AE which started at anytime from the date of the screening visit up to and including 30 days after the last day of study medication. A serious adverse event (SAE) occurring during the interval on therapy and within 30 days post therapy was defined as an SAE which started at anytime from the date of the screening visit up to and including 30 days after the last day of study medication.		
	<b>Amoxicillin / clavulanate SR 2000 / 125mg bid (N=307)</b>	<b>Levofloxacin 500mg od (N=315)</b>
<b>Most Frequent Adverse Events – On-Therapy Plus 30 Days Post-Therapy</b>	<b>n (%)</b>	<b>n (%)</b>
Subjects with any AE(s), n (%)	111 (36.2)	116 (36.8)
Diarrhoea	41 (13.4)	13 (4.1)
Nausea	14 (4.6)	18 (5.7)
Headache	8 (2.6)	7 (2.2)
Abdominal pain	5 (1.6)	6 (1.9)
Cardiac failure	5 (1.6)	0
Dizziness	5 (1.6)	4 (1.3)
Moniliasis	5 (1.6)	4 (1.3)
Pharyngitis	5 (1.6)	4 (1.3)
Rhinitis	5 (1.6)	8 (2.5)

Bronchitis	4 (1.3)	5 (1.6)
Chest pain	4 (1.3)	1 (0.3)
Dyspnoea	4 (1.3)	3 (1.0)
Viral infection	4 (1.3)	2 (0.6)
Vomiting	4 (1.3)	3 (1.0)
Chronic obstructive airways disease	3 (1.0)	4 (1.3)
Arthralgia	2 (0.7)	6 (1.9)
Asthenia	2 (0.7)	4 (1.3)
Back pain	2 (0.7)	6 (1.9)
Injury	2 (0.7)	7 (2.2)
Myalgia	2 (0.7)	4 (1.3)

**Serious Adverse Events - On-Therapy Plus 30 Days Post-Therapy**  
**n (%) [n considered by the investigator to be related to study medication]**

	<b>Amoxicillin / clavulanate SR 2000 / 125mg bid (N=307)</b>	<b>Levofloxacin 500mg od (N=315)</b>
Subjects with non-fatal SAEs, n (%)	10 (3.3)	13 (4.1)
	<b>n (%) [related]</b>	<b>n (%) [related]</b>
Neoplasm, not otherwise specified	2 (0.7) [0]	0
Pneumonia	2 (0.7) [0]	0
Chronic obstructive airways disease	1 (0.3) [0]	2 (0.6) [0]
Dyspnoea	1 (0.3) [0]	1 (0.3) [0]
Anxiety	1 (0.3) [0]	0
Cardiac failure	1 (0.3) [0]	0
Delirium	1 (0.3) [0]	0
Dizziness	1 (0.3) [0]	0
Respiratory insufficiency	1 (0.3) [0]	0
Injury	0	2 (0.6) [0]
Abscess	0	1 (0.3) [0]
Asthma	0	1 (0.3) [0]
Bronchitis	0	1 (0.3) [0]
Atrial fibrillation	0	1 (0.3) [0]
Haematoma	0	1 (0.3) [0]
Infection	0	1 (0.3) [0]
Oedema dependent	0	1 (0.3) [0]
Respiratory disorder	0	1 (0.3) [1]
Syncope	0	1 (0.3) [0]
Subjects with fatal SAEs, n (%)	0	0

**Conclusion:**

See publications below.

**Publications:**

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.

File T, Sethi S, Jacobs M, Anzueto A, Twynholm M, Pypstra R. Comparative efficacy and safety of pharmacokinetically enhanced amoxicillin/clavulanate vs levofloxacin in AECB. Abstracts from the 98th Annual Meeting of the American Thoracic Society, Atlanta, GA, USA. May 2002, page B28, Abstract 312.

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. 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. --- Abstracts from the 41st Annual Meeting of the Infectious Disease Society of America, San Francisco, USA. October 2003, page 84, Abstract 303.

S. Miller, M. Twynholm, E. Berkowitz, S. Gormley, A. White, L.A. Miller, C. Jakielaszek. Bacteriological outcomes with pharmacokinetically enhanced amoxicillin/clavulanate (2000/125 mg) in patients with community-acquired respiratory infection caused by *Streptococcus pneumoniae*, including drug-resistant (DRSP) strains. Abstracts from the 15th European Congress of Clinical Microbiology and Infectious Diseases, April 2005.

File T, Garau J, Jacobs MR, Wynne B. Pharmacokinetically enhanced amoxicillin/clavulanate 2000/125 mg in the treatment of community-acquired pneumonia (CAP) caused by *Streptococcus pneumoniae*, including penicillin-resistant strains. *Int J Antimicrob Agents* 2005; 25(2):110–119.

Date Updated: 30-Oct-2005