

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.

| |
|--|
| Study No.: 314 |
| Title: A Comparison of the Efficacy and Safety of Augmentin 45/6.4 mg/kg/day in Divided Doses q12h for 10 days, Augmentin 45/6.4 mg/kg/day in Divided Doses q12h for 5 days, and Augmentin 40/10 mg/kg/day in Divided Doses q8h for 10 days in the Treatment of Acute Otitis Media in Children. |
| Rationale: At the time of this study, in the United States and Canada, Augmentin (amoxicillin/clavulanate) was dosed at 40/10 mg/kg/day in divided doses every (q) 8 hours (h) (three times a day; TID) for the treatment of acute otitis media (AOM). The main purpose of this study was to determine whether the administration of a new 7:1 formulation of amoxicillin/clavulanate (45/6.4 mg/kg/day) in divided doses every 12 hours (two times a day; BID) for 5 or 10 days resulted in clinical efficacy rates within 15% of that for the approved 40/10 mg/kg/day every 8 hours dosing regimen. |
| Phase: III |
| Study Period: 31 January 1994 to 22 June 1994. |
| Study Design: A randomized, single blind (investigator blind), multicenter, comparative study. Subjects were instructed to attend the clinic at the preliminary visit (Day -1 to 0), end of therapy visit (Day 12-14) and follow up visit (Day 32-38). In addition, an on-therapy telephone visit (Day 3-5) and optional interim visit (day 2-10) were included in a subject's participation in the study. |
| Centers: 24 centers in Canada (5) and United States (19). |
| Indication: Acute otitis media in children |
| Treatment: Subjects were randomized equally (1:1:1 ratio) to one of three treatment groups: TID 10-day regimen: 40/10 mg/kg/day amoxicillin/clavulanate ('125' or '250' oral suspensions) in divided doses every 8 hours for 10 days. BID 5-day regimen: 45/6.4 mg/kg/day amoxicillin/clavulanate ('200' or '400' oral suspensions) in divided doses every 12 hours for 5 days. BID 10-day regimen: 45/6.4 mg/kg/day amoxicillin/clavulanate ('200' or '400' oral suspensions) in divided doses every 12 hours for 10 days. |
| Objectives: The primary objective was to compare the efficacy and safety of amoxicillin/clavulanate 45/6.4 mg/kg/day BID for 5 or 10 days with amoxicillin/clavulanate 40/10 mg/kg/day TID for 10 days in the treatment of AOM in children. The secondary objective was to compare the incidence of adverse experiences, particularly diarrhea, among the three treatment groups where the ratio of clavulanate potassium to amoxicillin for the bid regimen was reduced from 1:4 to 1:7 and the total daily dose of clavulanate potassium was reduced by one third. |
| Primary Outcome/Efficacy Variable: Clinical response (success or failure) to therapy at follow-up (Days 32 to 38). Clinical success was defined as sufficient resolution of AOM such that no additional antibacterial therapy for AOM was indicated. Clinical failure at follow up was defined as reappearance or deterioration of AOM following clinical success at end of therapy. If a patient was deemed to be a clinical failure at any stage, this outcome was carried forward to all further visits. |
| Secondary Outcome/Efficacy Variable(s): Clinical response (success or failure) to therapy at end of therapy (Days 12 to 14). Clinical success was defined as sufficient resolution of AOM such that no additional antibacterial therapy AOM was indicated. Clinical failure was recorded when there was insufficient improvement of AOM at end of therapy requiring additional antibacterial therapy. Protocol defined diarrhea (PDD) was defined as three or more watery stools in one day or two or more watery stools per day for two consecutive days during Days 1-11, as recorded in patient diaries. Additionally, any event of diarrhea noted by the investigator as an adverse event leading to withdrawal was included as a PDD event in this analysis, even if not recorded in patient diaries. |
| Statistical Methods: The intent-to-treat (ITT) population included all subjects who were randomized to receive study medication. The intent-to-treat bowel habit population included all subjects who were randomized to receive study medication and for whom bowel habit data were available. The per protocol (PP) population included subjects who were administered study medication, had pre- and post-therapy assessments and did not make any of the protocol violations specific to that assessment. Safety assessments were carried out on the ITT population, except for PDD, which was carried out on the intent-to-treat bowel habit population. The primary efficacy analysis in this study was performed on the PP population. The efficacy variables, categorized as either clinical success or failure, were analyzed using two-sided 95% confidence intervals (CIs) constructed using the normal approximation to the binomial distribution for differences in response rates (BID 10-day minus TID 10-day and BID 5-day minus TID 10-day) at the |

| | | | |
|---|--|--|---|
| end of therapy and at follow-up. For the primary efficacy variable, the BID 10 days or BID 5 days treatment groups were considered 'equivalent' to the TID 10 days group if the lower limit of the 95% CI did not fall below -15%. It should be noted that the study was not designed to demonstrate non-inferiority for secondary end-points where the numbers of patients was too small to draw any conclusions. There were no adjustments for multiple comparisons, timepoints or endpoints. | | | |
| Study Population: Male or female subjects, aged between 2 months and 12 years inclusive, who were diagnosed with AOM based on otoscopic findings, were eligible for inclusion in the study. Subjects with spontaneous perforation of the tympanic membrane, subjects with anatomic abnormalities associated with middle ear effusion (MEE) and subjects with concomitant infection were excluded. . | | | |
| | TID 10-day 40/10mg/kg/day | BID 5-day 45/6.4mg/kg/day | BID 10-day 45/6.4mg/kg/day |
| Number of Subjects: | | | |
| Planned, N | 200 | 200 | 200 |
| Randomized, N | 288 | 293 | 287 |
| PP Population at Follow-Up, N | 148 | 161 | 149 |
| Completed, n (%) | 245 (85.1) | 264 (90.1) | 252 (87.8) |
| Total Number Subjects Withdrawn, n (%) | 43 (14.9) | 29 (9.9) | 35 (12.2) |
| Withdrawn due to Adverse Events, n (%) | 24 (8.3) | 9 (3.1) | 16 (5.6) |
| Withdrawn due to Lack of Efficacy, n (%) | 1 (0.3) | 7 (2.4) | 2 (0.7) |
| Withdrawn for Other Reasons, n (%) | 18 (6.3) | 13 (4.4) | 17 (5.9) |
| Demographics | TID 10-day 40/10mg/kg/day | BID 5-day 45/6.4mg/kg/day | BID 10-day 45/6.4mg/kg/day |
| N (ITT) | 288 | 293 | 287 |
| Females: Males | 148: 140 | 135: 158 | 148: 139 |
| Mean Age, years (SD) | 3.0 (2.8) | 2.8 (2.7) | 2.9 (2.7) |
| White, n (%) | 247 (85.8) | 252 (86.0) | 246 (85.7) |
| Primary Efficacy Results: (PP Population at Follow-up) | | | |
| Clinical response to therapy at follow-up (Days 32-38): | TID 10-day 40/10mg/kg/day (N=148) | BID 5-day 45/6.4mg/kg/day (N=161) | BID 10-day 45/6.4mg/kg/day (N=149) |
| Success, n (%) | 95 (64.2) | 93 (57.8) | 94 (63.1) |
| Failure, n (%) | 53 (35.8) | 68 (42.2) | 55 (36.9) |
| Treatment difference (BID 10-day vs TID 10-day) | -1.10 | | |
| 95% CI | -12.04, 9.84 | | |
| p-value | 0.164 | | |
| Treatment difference (BID 5-day vs TID 10-day) | -6.43 | | |
| 95% CI | -17.28, 4.43 | | |
| p-value | 0.085 | | |
| Secondary Outcome Variable(s): (PP Population at end of therapy) | | | |
| | TID 10-day 40/10mg/kg/day (N=189) | BID 5-day 45/6.4mg/kg/day (N=197) | BID 10-day 45/6.4mg/kg/day (N=178) |
| Clinical response at end of therapy (Days 12-14): | | | |
| Success, n (%) | 149 (78.8) | 140 (71.1) | 154 (86.5) |
| Failure, n (%) | 40 (21.2) | 57 (28.9) | 24 (13.5) |
| Treatment difference (BID 10-day vs TID 10-day) | 7.68 | | |
| 95% CI | -0.01, 15.37 | | |
| Treatment difference (BID 5-day vs TID 10-day) | -7.77 | | |
| 95% CI | -16.37, 0.83 | | |
| Safety Results: ITT Population – Adverse events (AEs) and serious AEs (SAEs) were collected that occurred during the study from the point of randomization until follow-up. AEs and SAEs reported on-therapy and up to 30 days post-therapy were summarized. | | | |
| | TID 10-day 40/10mg/kg/day (N=288) | BID 5-day 45/6.4mg/kg/day (N=293) | BID 10-day 45/6.4mg/kg/day (N=287) |

| Most Frequent Adverse Events – On-Therapy plus 30 Days Post-Therapy | | | |
|---|--|--|---|
| Subjects with any AE(s), n (%) | 180 (62.5) | 169 (57.7) | 168 (58.5) |
| Coughing | 36 (12.5) | 36 (12.3) | 33 (11.5) |
| Vomiting | 31 (10.8) | 21 (7.2) | 29 (10.1) |
| Rhinitis | 26 (9.0) | 26 (8.9) | 26 (9.1) |
| Upper respiratory tract infection | 24 (8.3) | 23 (7.8) | 23 (8.0) |
| Fever | 15 (5.2) | 20 (6.8) | 20 (7.0) |
| Pharyngitis | 20 (6.9) | 13 (4.4) | 16 (5.6) |
| Diarrhea considered serious or leading to withdrawal | 28 (9.7) | 18 (6.1) | 15 (5.2) |
| Dermatitis, contact | 26 (9.0) | 14 (4.8) | 13 (4.5) |
| Therapeutic response increased (accidental overdose) | 3 (1.0) | 13 (4.4) | 10 (3.5) |
| Rash | 11 (3.8) | 11 (3.8) | 10 (3.5) |
| Abdominal pain | 11 (3.8) | 15 (5.1) | 6 (2.1) |
| Incidence of protocol-defined diarrhea (PDD) | TID 10-day 40/10mg/kg/day n/N (%) | BID 5-day 45/6.4mg/kg/day n/N (%) | BID 10-day 45/6.4mg/kg/day n/N (%) |
| Intent-to-treat bowel habit population | 74/277 (26.6) | 25/286 (8.7) | 27/280 (9.6) |
| Serious Adverse Events - On-Therapy plus 30 Days Post-Therapy n (%) [n considered by the investigator to be related to study medication] | | | |
| | TID 10-day 40/10mg/kg/day (N=288) | BID 5-day 45/6.4mg/kg/day (N=293) | BID 10-day 45/6.4mg/kg/day (N=287) |
| Subjects with non-fatal SAEs, n (%) | 3 (1.0) | 13 (4.4) | 11 (3.8) |
| | n (%) [related] | n (%) [related] | n (%) [related] |
| Therapeutic response increased (accidental overdose) | 3 (1.0) [3] | 13 (4.4) [13] | 10 (3.5) [8] |
| Diarrhea | 0 | 0 | 2 (0.7) [2] |
| Vomiting | 0 | 0 | 1 (0.3) [1] |
| Aggressive reaction | 1 (0.3) [0] | 0 | 0 |
| Infection bacterial | 0 | 0 | 1 (0.3) [0] |
| Glomerulonephritis | 0 | 1 (0.3) [0] | 0 |
| Subjects with fatal SAEs, n (%) | 0 | 0 | 0 |

Conclusion:

See publication below.

Publications:

Hoberman A, Paradise J, Burch D, Valinski W, Hedrick J, Aronovits G, Drehobl M, Rogers JM. Equivalent efficacy and reduced occurrence of diarrhea from a new formulation of amoxicillin/clavulanate potassium (Augmentin®) for treatment of acute otitis media in children. *Pediatr Infect Dis J* 20(5): 463-470.

Improved Safety Profile of New Pediatric Amoxicillin/Clavulanate in Acute Otitis Media, Aronovitz, G, MD; Hoberman, A, MD; Drehobl, M, MD; Hedrick, J, MD. Atlanta, Georgia; Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; Centre for Health Care, San Diego, California; Physicians for Children and Adolescents, Bardstown, Kentucky; San Francisco, CA; USA. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). 9/17/1995

Date Updated: 03-Aug-2005