BRISTOL-MYERS SQUIBB COMPANY
Pharmaceutical Research Institute

A Multi-Investigator Randomized Trial
Comparing the Efficacy of Cefprozil
Versus Amoxicillin/Clavulanate Potassium
in the Treatment of Acute Otitis Media
in Children
Protocol AI414-065

FINAL STUDY REPORT
Study 414-065

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PRINCIPAL INVESTIGATORS: Multiple (See Appendix B-2)
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This open, multi-investigator, randomized clinical trial was designed to evaluate the safety and efficacy of cefprozil administered orally for 10 days at 30 mg/kg/day in two equally divided doses (oral suspension) versus AMOX/CLAV administered orally for 10 days at 40 mg/kg/day in three equally divided doses (oral suspension) as treatment for acute and uncomplicated otitis media in patients at least six months old. The trial was also to evaluate the frequency of persistent effusion.

Demography:
Fourteen principal investigators enrolled a total of 529 patients who received 530 courses of therapy. (Patient 44 at study center 2 was also enrolled as patient 81 at the same center. During the first enrollment this patient was diagnosed with H. influenzae [p-] and received cefprozil. During the second enrollment this patient was diagnosed with M. catarrhalis [p+] and received AMOX/CLAV. Both courses of therapy are evaluable for efficacy.) Patients were enrolled at each center and assigned treatment according to a 1:1 (cefprozil:amoxicillin/clavulanate) randomization schedule: 263 patients (168 (64%) evaluable for efficacy) in the cefprozil group and 267 (166 (62%) evaluable for efficacy) in the AMOX/CLAV group. Of the 168 evaluable cefprozil patients, 80 (48%) were female and 88 (52%) were male; 32 (19%) were black, 13 (8%) Hispanic, one (1%) Oriental, 121 (72%) white, and one (1%) other (mulatto). Patient ages ranged from 0.5 to 9.0 (median 2.0) years. Of the 166 evaluable AMOX/CLAV patients, 70 (42%) were female and 96 (58%) were male; 25 (15%) were black, 17 (10%) Hispanic, and 124 (75%) white. Patient ages ranged from 0.5 to 10.0 (median = 1.0) years (Table 5.4.2.1; Appendix D-5).

Intervention:
Ten days of dosing were recommended, but a minimum of 18 doses of cefprozil, missing less than two consecutive doses, or 27 doses of AMOX/CLAV, missing less than three consecutive doses, was required for the efficacy evaluation. In the cefprozil group 114 (68%) evaluable patients received the recommended 20 doses; in the AMOX/CLAV group 81 (49%) evaluable patients received the recommended 30 doses (Table 5.4.3; Appendix D-12).

Efficacy:
Cefprozil was effective in 141 (84%) of the 168 evaluable patients and partially effective in 1 (1%) and ineffective in 26 (15%). AMOX/CLAV was effective in 129 (78%) of the 166 evaluable patients, partially effective
in 7 (4%), and ineffective in 30 (18%) (Table 5.4.5.3B; Appendix D-18).
Safety:
All 263 cefprozil patients and all 267 AMOX/CLAV patients were evaluable for safety. No deaths occurred in either group. Two (<1%) of the 263 patients in the cefprozil group discontinued therapy because of ACR. Two (<1%) of the 267 patients in the AMOX/CLAV group discontinued because of ACR.

Patients Less Than 3 Years of Age: Thirty-six (23%) of the 160 cefprozil patients less than 3 years of age reported a total of 45 ACR. Twenty-eight of the ACR were considered probably related to the study drug, and 15 were of unknown relationship to study drug. Those ACR probably related to cefprozil and occurring in more than 1% of patients were 7 cases of diarrhea, 6 cases of diaper rash, 5 cases of loose stool, and 2 cases each of skin rash and rash (monilial). Those ACR of unknown relationship and occurring in more than 1% of patients were 5 cases of diarrhea, 5 cases of vomiting, and 2 cases of rash.

Sixty (34%) of the 160 AMOX/CLAV patients less than 3 years of age reported a total of 86 ACR. Sixty-nine of the ACR were considered probably related to the study drug, and 9 were of unknown relationship to study drug. Those ACR probably related to AMOX/CLAV and occurring in more than 1% of patients were 34 cases of diarrhea, 8 of diaper rash, 6 of rash (monilial), 4 of loose stool, and 3 each of vomiting and rash (Candida) and 2 of rash (yeast). The ACR of unknown relationship and occurring in more than 1% of patients were 6 cases of diarrhea (Table 5.5.4; Appendices D-24 and D-25).

For patients less than 3 years of age, there were statistically significant differences between the two treatment groups for the incidence of ACR (p = 0.008) and the number of patients who had at least one ACR considered either related or of unknown relationship to study drug (p = 0.016); cefprozil patients had significantly fewer ACR than AMOX/CLAV patients (Appendix C-1).

Patients 3 Years of Age and Older: Ten (10%) of the 103 cefprozil patients 3 years of age or older reported a total of 10 ACR. Five of the ACR were considered probably related to the study drug, and 3 were of unknown relationship to study drug. Those ACR probably related to cefprozil and occurring in more than 1% of patients were 2 cases of vomiting. No ACR of unknown relationship occurred in more than 1% of patients.
Twenty (19%) of the 104 AMOX/CLAV patients 3 years of age or older reported a total of 24 ACE. Seventeen of the ACE were considered probably related to the AMOX/CLAV and 3 were of unknown relationship. Those ACE probably related to AMOX/CLAV and occurring in more than 1% of patients were 11 cases of diarrhea. The ACE of unknown relationship and occurring in more than 1% of patients were two cases of diarrhea (Table 5.5.4; Appendices D-24 and D-25).

For patients 3 years of age or older, there was no significant difference between the two treatment groups for the incidence of ACE (p = 0.167) nor for the incidence of drug-related ACE (p = 0.137).

Laboratory screening detected no unusual effects of either drug on patient physiology. (Tables 5.5.5.1A and 5.5.5.1B; Appendix E-3).

**Susceptibility:**
Four hundred seventy pathogens were isolated and tested for sensitivity. Four hundred thirty-four of the 470 (92%) isolates were susceptible to cefprozil, 26 (6%) displayed intermediate sensitivity, and 12 (3%) were resistant (Table 5.6A; Appendix F-1).

**Conclusions:**
Effective Overall Response to cefprozil (84%) at a dose of 30 mg/kg/day was equal to the Effective Overall Response to AMOX/CLAV (78%) at a dose of 40 mg/kg/day in treating otitis media infections. There were statistically significant differences between the two treatment groups for patients less than 3 years of age in both the incidence of ACE and the incidence of drug-related ACE; cefprozil patients had significantly fewer ACS than AMOX/CLAV patients. The majority (92%) of pathogens isolated from the patients were susceptible to cefprozil.