Date: May 19, 2010

RE: Aztreonam clinical trial in pediatric population.

Statement by Lilit KHATCHIKIAN, MD

Bristol-Myers Squibb, Co. (BMS) has produced this medical statement in response to a request dated on April 20, 2010, from the European Medical Agency (EMEA) related to the European Union work-sharing procedure for pediatric studies to be submitted according to article 45 of the EU- Regulation No 1901/2006 as amended.

In the line listings provided in January 2008 eight documents relative to the studies on aztreonam in pediatric population, which were not submitted previously, were identified. On reviewing these two have been found to be simply memos with replacement/updated pages to previously submitted reports. These pages made no changes to the overall conclusions. The remaining documents are summarized below.


A prospective randomized, open study was conducted in the Neonatal Intensive Care Unit at the National Children's Hospital, San José, Costa Rica.
Objective

The study was designed to evaluate aztreonam plus ampicillin versus conventional therapy with amikacin and ampicillin for treatment of septic neonates.

Treatment design

Infants in the Neonatal Intensive Care Unit of the National Children's Hospital, San Jose, Costa Rica with suspected or documented sepsis were eligible for enrollment. Those patients with hepatic or renal dysfunction or with suspected or documented infection caused by *Staphylococcus*, anaerobes, *Listeria monocytogenes*, or aerobic Gram positive cocci were excluded from enrollment.

Patients assigned to receive conventional therapy were given amikacin intravenously, 7.5 mg/kg every 12 hours for neonates less than 2000 grams and younger than 7 days of age and 10 mg/kg every 12 hours or every 8 hours for those younger than 7 days greater than 2,000 grams or older than 7 days of age.

Ampicillin 50 mg/kg was given intravenously every 12 hours to infants younger than 7 days of age and weighing less 2000 grams, every 8 hours for those younger than 7 days of age with a birthweight greater than 2000 grams or more than 7 days, and less than 2000 grams, and every 6 hours to infants weighing 2000 grams or more, and older than 7 days.

Aztreonam 30 mg/kg was given every 12 hours to neonates younger than 7 days and a birthweight less than 2000 grams, every 8 hours to neonates with a birthweight greater than 2000 grams, and younger than 7 days, and every 6 hours to infants older than 7 days of age independent of birthweight.

The minimum duration of treatment for patients with documented bacterial infection was 10 days. Treatment was prolonged when signs and symptoms of infection persisted and in patients with central nervous system infection who received a minimum of 14 to 21 days of treatment depending on the etiologic agent and clinical condition.

Evaluation of safety: The following laboratory tests were performed at the time of enrollment, every 3 to 5 days during treatment, and at the end of treatment: Hemoglobin concentration, urinalysis, complete blood cell count and differential and alanine
aminotransferase, creatinine, protein, and total and fractional bilirubin concentrations in serum. In those with abnormal values at the end of treatment, the tests were periodically repeated until normal or stable.

**Laboratory studies:** Cultures of blood, cerebrospinal fluid (CSF), urine, tracheal aspirate obtained on first intubation, and soft tissue, when involved, were obtained from study patients. Sites of positive culture were recultured daily, whenever possible, until sterile.

**Susceptibility testing:** In-vitro susceptibilities of the bacteria recovered from blood, CSF or other sites were determined for aztreonam, amikacin and ampicillin by standard microtiter technique.

**Size of the studied population:**

From May 1985 through June 1986, one hundred and forty-seven (147) patients were enrolled in the study; 75 patients received aztreonam and ampicillin and 72 received amikacin and ampicillin (conventional therapy).

**Results:**

Sixty patients were evaluated. Twenty-eight aztreonam and ampicillin treated patients and 32 conventionally treated patients had bacteriologically documented infection caused by Gram-negative enteric bacilli or *Pseudomonas* species. Treatment groups were comparable regarding age, birthweight, duration of symptoms, number with shock, prior antibiotic therapy, and clinical status at the time of enrollment. Bronchoneumonia and infections caused by *Pseudomonas* species occurred in significantly more patients in the amikacin and ampicillin group compared with patients given aztreonam and ampicillin. Septicemia was documented in 83% of each treatment group and Gram negative enteric bacilli and *Pseudomonas* species were the principal pathogens. Median peak serum bactericidal titers against the etiologic agent were 1:64 for the aztreonam and ampicillin and 1:16 for amikacin and ampicillin-treated patients, respectively. No clinical adverse reactions were observed in either group. Case fatality rates resulting from the primary infection were 7% and 22% (P=0.011), superinfection occurred in 39% and 34%, and treatment failure was documented in 7% and 28% (P=0.036) of the aztreonam and ampicillin and conventionally treated patients, respectively.
Based on these results aztreonam appears to be comparably effective to amikacin when used initially with ampicillin for empiric treatment of neonatal bacterial infections.

2. Pediatric Supplement (patient doses in the 2-12 year old age group)

Protocols 18554-58, -64, and -130

Case report forms received in-house since the data lock date of June 1986 for protocols 18554-58, -64, and -130 have been reviewed specifically for patient doses in the 2-12 year old age group. A breakdown of the doses is specified below by protocol.

Protocol 18554-58

Ninety-two case report forms have been received since the data lock date. Thirty-six of these cases were of patients within the 2-12 year old age group. The doses and their indications of all 36 patients are shown in the table below. It is important to note, however, that evaluability has not been assessed to date on these cases.

Breakdown of Pediatric Patients

Cases Received Since June 1986 Data Lock

<table>
<thead>
<tr>
<th>Protocol 18554-58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
</tr>
<tr>
<td>Meningitis</td>
</tr>
<tr>
<td>Lower Respiratory Tract Infections</td>
</tr>
</tbody>
</table>

All of these patients had experienced a complete clinical cure of their disease symptoms with the exception of one patient. This patient died as a result of the progression of his
gram-negative meningitis. This death was in no way attributed to his two day therapy with aztreonam.

No serious adverse events were noted in any of the patients listed on the previous table. One patient, however, experienced a transient rise in SGOT which returned to pretreatment levels following completion of the course of therapy.

Protocol 18554-64

Five case report forms have been received since the June 1986 data lock date. Although the only pediatric patient of these 5 cases was unevaluable for efficacy, the aztreonam dose is worthy of mention. This patient received 19.6 mg/kg aztreonam dose every 6 hours for treatment of acute pulmonary exacerbation in cystic fibrosis. This patient enjoyed a satisfactory clinical outcome.

Protocol 18554-130

Four pediatric patients were treated under this comparative trial in cystic fibrosis, three of which were evaluable for efficacy. The aztreonam doses for all four patients in the treatment of acute pulmonary exacerbations were between 50-60 mg/kg/dose every 6 hours. All four patients had tolerated the medication well and had experienced either a partial or complete clinical cure.

3. Evaluations of efficacy of Aztreonam in treatment of cystic fibrosis (in response to a request from FDA)

Additional evaluations of efficacy of aztreonam in the treatment of cystic fibrosis in pediatric patients (ten years or younger), by protocol, were as follows:

Protocol 18554-130

The objective of this study was to evaluate and compare the efficacy and safety of aztreonam to that of the combination therapy of tobramycin plus azlocillin in the treatment of acute pulmonary exacerbations in patients with cystic fibrosis. Thirty-one cystic fibrosis patients with gram-negative bacterial pulmonary infections (due predominantly to *Pseudomonas aeruginosa*) were treated under this protocol. Of these patients, three had met the following criteria: (1) ten years of age or younger; (2)
randomized to receive aztreonam therapy, and (3) evaluable for efficacy. These patients, along with their clinical and microbiologic response, are listed in the table below.

Evaluative Aztremenam Patients Ten Years or Younger

**Protocol 18554-130**

Cystic Fibrosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Race</th>
<th>Sex</th>
<th>Specific Diagnosis</th>
<th>Total Dose (g)</th>
<th>Total Days (Rx)</th>
<th>Organisms (#Isolates)</th>
<th>Micro Response</th>
<th>Clinical Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>014</td>
<td>6</td>
<td>C</td>
<td>M</td>
<td>Pneumonia</td>
<td>89.3</td>
<td>29</td>
<td><em>P. aeruginosa</em> (2)</td>
<td>Failure</td>
<td>Partial Cure</td>
</tr>
<tr>
<td>016</td>
<td>10</td>
<td>C</td>
<td>F</td>
<td>Pneumonia</td>
<td>60.0</td>
<td>15</td>
<td><em>P. aeruginosa</em> (2)</td>
<td>Cure</td>
<td>Cure</td>
</tr>
<tr>
<td>020</td>
<td>10</td>
<td>C</td>
<td>M</td>
<td>Pneumonia</td>
<td>140.0</td>
<td>14</td>
<td><em>P. aeruginosa</em> (2)</td>
<td>Cure</td>
<td>Cure</td>
</tr>
</tbody>
</table>

All three patients enjoyed a satisfactory clinical outcome. Satisfactory microbiologic outcomes were also observed for two of the three patients. To reference the single microbiologic failure among the group, susceptibility testing performed on these two isolates throughout the therapy course had indicated a decreasing susceptibility to aztreonam. Resistance, defined by a minimal inhibitory concentration of 32µg/ml or greater, was detected at day 29. Therapy was discontinued at the time of the submission of this supplement (August 1998).

NOTE: A fourth pediatric patient, age 8, was similarly treated with aztreonam under this protocol. However, this patient was unevaluable for efficacy evaluation as a susceptible pathogen had not been obtained within 48 hours of therapy initiation.

All patients had tolerated the study medication well. No adverse events had been reported.
Protocol 18554-64

Since the submission of this document, five additional patients have been treated under this protocol. One patient, age 9, was within the age group of interest at this time. This patient, however, was unevaluable for efficacy as the case report form did not specify study drug susceptibility. This patient received aztreonam for a total of 29 days and enjoyed a satisfactory clinical outcome following therapy. This patient had tolerated the study medication well and had reported no adverse events.

4. Evaluations of efficacy of aztreonam in treatment of cystic fibrosis (data from protocols 18554-130 and 18554-64 in pediatric patients)

In this document six publications on the treatment of patients with cystic fibrosis were provided. Two publications were on aztreonam and are summarized below:


A noncomparative pilot study was conducted to assess the potential usefulness of aztreonam in pulmonary exacerbations of cystic fibrosis. Of 27 patients initially enrolled 25 received sufficient courses of aztreonam therapy to be evaluable. All patients received 200 mg/kg/day of aztreonam in 4 equally divided doses administered intravenously. Of 57 isolates of Pseudomonas aeruginosa from pretherapy sputum cultures, 48 were susceptible to aztreonam in vitro as were 11 of 18 strains isolated at the conclusion of therapy. With treatment colony counts of P. aeruginosa in sputum were reduced by 3 log_{10}, or more in 15 patients. It was totally (but temporarily) eradicated in 11 of these patients. Clinical scores and white blood cell counts improved significantly (P < 0.05). Side effects of aztreonam were limited to transient elevations of liver enzymes occurring in 16 patients. The authors concluded that aztreonam merits further evaluation in a randomized, comparative trial with standard antibiotic therapy for cystic fibrosis.


Twelve patients who underwent 26 episodes of lower respiratory tract infection due to Pseudomonas Aeruginosa were treated with aztreonam. Infectious episodes were severe
in 11 patients, moderate in 10 patients, and mild in 5 patients. In 85% of the episodes, significant clinical improvement occurred, but in four severe episodes, the clinical response was unsatisfactory. The mean interval between initiation of treatment and improvement was seven days. Aztreonam was as clinically effective in the treatment or infections due to organisms susceptible to penicillins active against Pseudomonas as it was in the treatment of infections due to organisms resistant to these agents. Pseudomonas Aeruginosa was not permanently eradicated from the sputum of any of the patients treated with aztreonam. It did not cause any major adverse effects, and the only laboratory abnormality found was an increase in alkaline phosphatase, which occurred during 12 (46%) courses of therapy. Levels of alkaline phosphatase returned to normal after conclusion of treatment. Aztreonam was shown to be clinically effective in the treatment of lower respiratory infections due to Pseudomonas Aeruginosa in patients with cystic fibrosis.


The purpose of this study addendum was to assess the aztreonam pharmacokinetics in premature pediatric patients receiving multiple doses.

Twenty-six patients were enrolled in this study of aztreonam pharmacokinetics in pediatric patients suspected of having systemic infections and treated presumptively. In all patients, infection was ruled out by negative microbiologic culture results obtained following study enrollment. Patients ranged in age from 1 to 4 days and in weight from 0.7 to 2.0 kg at the time enrollment.

All patients were treated with aztreonam, 30mg/kg, administered as 15 minute infusions every 12 hours.

The mean serum concentrations of aztreonam at the beginning (first dose, Day 1) and end (Days 3 to 4 of therapy) of study were similar, suggesting no significant accumulation of aztreonam given at a dose 30mg/kg every 12 hours.

The following pharmacokinetic parameters for aztreonam were determined: maximal serum concentration (Cmax), minimum serum concentration (Cmin), area under the serum concentration-time curve evaluated over one dose interval (AUC₀⁻→T), serum clearance (Cls) and serum elimination half-life (t₁/₂).
The mean serum half-life on Day 1 was 8.4 hours. Since aztreonam was given every 12 hours, an increase in serum levels might have occurred on Days 3 to 4 following multiple doses. Accumulation did not occur (as shown by the AUC_0→T values which were similar for Days 1 and 3 to 4) because the serum aztreonam clearance was higher on Days 3 to 4 than on Day 1. This more rapid clearance on Days 3 to 4 was reflected in the serum elimination half-life which tended to decrease between the beginning and the end of the study. These changes in the pharmacokinetic parameters can probably be explained by the physiologic changes that accompanied maturation during the period of study. The decreased clearance observed at the beginning of the study does not require dose adjustment because it is not of sufficient duration to cause accumulation of aztreonam during therapy.

Concentrations of aztreonam in the urine of patients enrolled in this study always exceeded the MIC of organisms considered sensitive to the drug.

The results of this study support the evaluation of aztreonam, 30 mg/kg, every 12 hours for the treatment of suspected systemic infections in premature neonatal patients.


This study was conducted according to Protocol No. 18544-32, Addendum A entitled “Single Intravenous-Dose Safety and Pharmacokinetic Study of Aztreonam (SQ 26,776) in Pediatric Patients”, dated July 26, 1984.

Objective:

The purpose of this study was to obtain safety and pharmacokinetic data on aztreonam and SQ 26,992 in pediatric patients. Each patient received a single 50-mg/kg dose of aztreonam by a 3-minute intravenous infusion. Serum and urine levels of aztreonam and SQ 26,992 were measured. Patients were carefully monitored for possible drug-related effects.

The study was conducted in Oklahoma Children’s Memorial Hospital.
Selection and Screening Procedures

The investigator selected 6 patients between the ages of 2 and 12 years for participation in this study. The patient numbers were assigned based upon the order of patient enrollment. Patients 1 to 31 were enrolled in Protocol 18554-32. Patients 32 to 37 were enrolled in this addendum.

Within 72 hours prior to the administration of aztreonam, a complete medical history and a physical examination were obtained. In addition, laboratory tests were performed in order to assess hematopoietic, hepatic and renal function:

Treatment design

Six (6) pediatric patients, hospitalized for various infectious or chronic diseases, were enrolled in this pharmacokinetic study. All patients had essentially normal renal function as judged by serum creatinine and blood urea nitrogen. Each patient received a single 3-minute infusion of aztreonam at a dose of 50mg/kg of body weight. The patients had physical examinations and a battery of clinical laboratory tests before and following drug administrations. They ranged in age from 3.0 to 11.9 years (mean age, 6.3 years) and weighted from 12.0 to 61.1kg (mean weight, 29.3kg).

Results

Aztreonam was well tolerated by all patients and no adverse reactions were noted.

Mean serum concentrations of aztreonam were 214.0, 109.1, 38.6 and 12.8 µg/ml at 0.25, 1, 3 and 6 hours after dosing, respectively (n=5, data from one patient were excluded because of possible mislabeling of samples).

Concentrations of SQ 26,992 (the open beta-lactum-ring metabolite of aztreonam) in serum were generally below the limit of detection of the assay).

Mean urine concentrations of aztreonam were 3297, 1660, 358, and 35 µg/ml during the 0-3, 3-6, 6-12, and 12-24 hour collection periods, respectively.

When expressed on a surface-area basis the mean serum clearance was similar to the values found in earlier studies of pediatric patients given 30mg/kg doses (Protocol 18554-32) and to those of normal adults given mean doses of 42mg/kg (Protocol 18554-1).
The pharmacokinetic data obtained in this study support clinical investigation of 50-mg/kg intravenous doses administrated every 6 hours for treatment of life-threatening infections in children aged 2-12 years who have normal renal function. Lower doses could be used to treat less serious infections.

The following documents were included in the line listings and have been found to contain only replacement/updated pages to previously submitted reports:

**Protocol 18554-62:** “Report of a single Intravenous-Dose Pharmacokinetic and Safety Study of aztreonam in Pediatric patients” (revised page to Appendix D 856710103). A footnote has been added to this page (September 1985).

**Protocols 18554-52 and Addendum A:** “Report of a single Intravenous-Dose Pharmacokinetic and safety study of aztreonam in pediatric patients given 30 or 50 mg/kg” (revised pages in 856771038). The mean 12.5-24.5 hour urinary aztreonam concentrations have been revised from 421.99 to 412.99 µg/ml (August 1985).

**Overall conclusion**

Based on this review the efficacy and safety information content in the current Company Core Data Sheet is still accurate and does not need to be updated.

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Global Pharmacovigilance & Epidemiology

Research & Development