These records are from CDER's historical file of information previously disclosed under the Freedom of Information Act (FOIA) for this drug approval and are being posted as is. They have not been previously posted on Drugs@FDA because of the quality (e.g., readability) of some of the records. The documents were redacted before amendments to FOIA required that the volume of redacted information be identified and/or the FOIA exemption be cited. These are the best available copies.

N 50608 -1

NDA

50-608

AP/LTR

[illegible]

[illegible]

[illegible], M.D.
Regulatory Affairs
[illegible]
[illegible]
[illegible]

Dear Dr. [illegible]:

Reference is made to your New Drug Application [illegible] submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for "[illegible]" (ampicillin sodium/sulbactam sodium) [illegible].

We also acknowledge receipt of your amendments [illegible] May [illegible], June [illegible], October [illegible], [illegible], [illegible], [illegible], February [illegible], [illegible], April [illegible], May [illegible], June [illegible], [illegible], July [illegible], August [illegible], September [illegible], [illegible], [illegible], October [illegible], and November [illegible], [illegible], [illegible].

We have completed our review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the [illegible] draft labeling submitted [illegible] December [illegible], [illegible]. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling. Marketing the product with FPL that is not identical to the draft labeling may render the product misbranded and an unapproved new drug. Please submit twelve copies of the FPL to FDA as soon as available. For administrative purposes this submission should be designated "FPL Supplement" to the approved NDA 50-608. Approval of this supplement by FDA is not required before labeling is used.

Should additional information relating to the safety and effectiveness of the drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

Please submit one market package of the drug when available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

[illegible]

[illegible], M.D.
[illegible]
[illegible]
[illegible]

NDA 50-608

SUMMARY BASIS OF APPROVAL

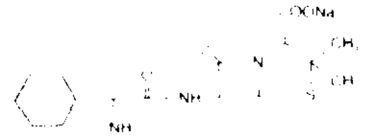
The medical officer's reviews and the pharmacology review will serve as the Summary Basis of Approval for the application 50-608 for UNASYN (ampicillin sodium/sulbactam sodium).

UNASYN

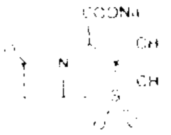
Ampicillin Sodium/Sulbactam Sodium

DESCRIPTION

[illegible]



[illegible]



[illegible]

CLINICAL PHARMACOLOGY

General: [illegible]

The following average levels of ampicillin and sulbactam were measured in the tissues and fluids listed:

TABLE A

Concentration of UNASYN in Various Body Tissues and Fluids

Fluid or Tissue	Dose (grams) Ampicillin/Sulbactam	Concentration (mcg/ml or mcg/g) Ampicillin/Sulbactam
Peritoneal Fluid	0.5/0.5 IV	[illegible]
Blister Fluid (Cantharides)	0.5/0.5 IV	8/20
Tissue Fluid	1/0.5 IV	[illegible]
Cerebrospinal Fluid (children with bacterial meningitis)	400/Mg/kg/day IV	[illegible]
Peritonsillar pus	2/0.5 IV	[illegible]
Intestinal mucosa	1.5/0.5 IV	11/18
Prostate	1/0.5 IM	[illegible]
Appendix	2/1 IV	[illegible]

MICROBIOLOGY

[illegible]

Gram-Positive Bacteria: [illegible]

Gram-Negative Bacteria: [illegible]

Anaerobes: [illegible]

Susceptibility Testing

Diffusion Technique: [illegible]

Dilution Techniques: Broth or agar dilution methods may be used to determine the minimal inhibitory concentration (MIC) value for susceptibility of bacterial isolates to ampicillin/sulbactam. [illegible]

The recommended dilution method employs a constant ampicillin/sulbactam ratio of 2:1 in all tubes with increasing concentrations of ampicillin. MIC's are reported in terms of ampicillin concentration in the presence of sulbactam at a constant 2 parts ampicillin to 1 part sulbactam.

Recommended UNASYN Susceptibility Ranges

	Resistant	Intermediate	Susceptible
Gram(-) and Staphylococcus			
Kirby-Bauer Zone Sizes	[illegible] mm	12-13 mm	14 mm
MIC (mcg of ampicillin/ml)	[illegible]	[illegible]	8
Hemophilus influenzae			
Kirby-Bauer Zone Sizes	[illegible] mm		20 mm
MIC (mcg of ampicillin/ml)	4		2

The non-beta-lactamase producing organisms which are normally susceptible to ampicillin, such as Streptococci, will have similar zone sizes as for ampicillin disks.

Staphylococci resistant to methicillin, oxacillin, or nafcillin must be considered resistant to UNASYN.

The quality control cultures should have the following assigned daily ranges for ampicillin/sulbactam:

		Disks	Mode MIC (mcg/ml ampicillin/mcg/ml sulbactam)
E. coli	(ATCC 25922)	20-24 mm	2/1
S. aureus	(ATCC 25923)	29-37 mm	0.12/0.06
E. coli	(ATCC 35218)	13-19 mm	8/4

*Performance standards for Antimicrobial Disk Susceptibility Tests [illegible] National Committee for Clinical Laboratory Standards, 771 East Lancaster Ave., Villanova, PA [illegible]

**Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically [illegible] National Committee for Clinical Laboratory Standards, 771 East Lancaster Ave., Villanova, PA [illegible]

INDICATIONS AND USAGE

UNASYN IV and IM is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.

Lower Respiratory Tract Infections caused by beta-lactamase producing strains of *Hemophilus influenzae*,* *Staphylococcus aureus** and *Branhamella catarrhalis*.

Skin and Skin Structure Infections caused by beta-lactamase producing strains of [illegible]

Urinary Tract Infections [illegible]

Intra-Abdominal Infections caused by beta-lactamase producing strains of [illegible] *Bacteroides* spp. (including *B. fragilis*) and *Enterobacter* spp.*

Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli** and *Bacteroides* spp.* (including *B. fragilis**).

*Evidence for this organism in this organ system was demonstrated in less than 10 infections.

While UNASYN is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify the organisms causing infection and to determine their susceptibility to UNASYN.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies, when there is reason to believe the infection may involve any of the beta-lactamase producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

CONTRAINDICATIONS

The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE

WARNINGS (cont'd)

CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving Pseudomonas or Candida), the drug should be discontinued and/or appropriate therapy instituted.

Laboratory Tests: While UNASYN possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function is advisable during prolonged therapy.

Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently.

Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with UNASYN.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.

Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

ADVERSE REACTIONS

UNASYN is generally well tolerated. The majority of side effects observed in clinical studies involving over 1,000 patients were transient in nature, and less than 1% of the patients discontinued treatment because of drug related side effects. The following adverse reactions have been reported:

Local Adverse Reactions

Pain at IM injection site — 16%
Pain at IV injection site — 3%
Thrombophlebitis — 3%

Systemic Adverse Reactions

The most frequently reported adverse reactions were diarrhea (3%) and rash in less than 2% of the patients.

Additional systemic reactions reported in less than 1% of the patients were: itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat and substernal pain, epistaxis and mucosal bleeding.

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hepatic: Increased SGOT, SGPT, alkaline phosphatase and LDH.
Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
Blood Chemistry: Decreased serum albumin and total proteins.
Renal: Increased BUN and creatinine.
Urinalysis: Presence of RBC's and hyaline casts in urine.

The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.

Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).

Hemic and Lymphatic Systems: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Overdosage: Neurological adverse reactions, including convulsions, may occur with the attainment of high CSF levels of beta-lactams. Ampicillin may be removed from circulation by hemodialysis. The molecular weight, degree of protein binding and pharmacokinetics profile of sulbactam suggest that this compound may also be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

UNASYN may be administered by either the IV or the IM routes.

For IV administration, the dose can be given by slow intravenous injection over at least 10-15 minutes, or can also be delivered in greater dilutions with 50-100 ml of a compatible diluent as an intravenous infusion over 15-30 minutes.

UNASYN may be administered by deep intramuscular injection. (See *Preparation for Intramuscular Use*.)

Adults: The recommended adult dosage of UNASYN is 1.5 g (1 g ampicillin as the sodium salt plus .5 g sulbactam as the sodium salt) to 3 g (2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt) every six hours. This 1.5 to 3 g range represents the total of ampicillin content plus the sulbactam content of UNASYN, and corresponds to a range of 1 g ampicillin/0.5 g sulbactam to 2 g ampicillin/1 g sulbactam. The total dose of sulbactam should not exceed 4 grams per day.

Impaired Renal Function

In patients with impairment of renal function the elimination kinetics of ampicillin and sulbactam are similarly affected, hence the ratio of one to the other will remain constant whatever the renal function. The dose of UNASYN in such patients should be administered less frequently in accordance with the usual practice for ampicillin and according to the following recommendations:

UNASYN Dosage Guide For Patients With Renal Impairment

Creatinine Clearance (ml/min/1.73m2)	Ampicillin/Sulbactam Half-Life (Hours)	Recommended UNASYN Dosage
≥30	1	1.5-3.0 g q 6h-q 8h
15-29	5	1.5-3.0 g q 12h
5-14	9	1.5-3.0 g q 24h

When only serum creatinine is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

$$\text{Males} \quad \frac{\text{weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}}$$

$$\text{Females} \quad 0.85 \times \text{above value}$$

COMPATIBILITY, RECONSTITUTION AND STABILITY

UNASYN sterile powder is to be stored at or below 30°C (86°F) prior to reconstitution.

When concomitant therapy with aminoglycosides is indicated, UNASYN and aminoglycosides should be reconstituted and administered separately, due to the *in vitro* inactivation of aminoglycosides by any of the aminopenicillins.

RECONSTITUTION

The following diluents may be used for reconstitution of UNASYN sterile powder for intravenous injection:

Sterile Water for Injection (USP)
0.9% Sodium Chloride Injection (USP)
5% Dextrose and 0.45% Sodium Chloride Injection (USP)
5% Dextrose Injection (USP)
10% Invert Sugar Injection
Lactated Ringer's Injection (USP)
Sodium Lactate Injection (USP) ⅙ Molar

The following diluents may be used for preparing solutions of UNASYN sterile powder for intramuscular injection:

Sterile Water for Injection (USP)
0.5% Lidocaine Hydrochloride Injection (USP)
2% Lidocaine Hydrochloride Injection (USP)

General Dissolution Procedures: UNASYN sterile powder for intravenous and intramuscular use may be reconstituted with any of the compatible solutions for infusion mentioned above. Solutions should be allowed to stand after dissolution to allow any foaming to dissipate to permit visual inspection for complete solubilization.

Preparation for Intramuscular Use: Consult the table below for recommended volumes to be added to vials to obtain solutions containing 375 mg UNASYN per ml (corresponding to 250 mg ampicillin/125 mg sulbactam per ml). Note: Use only freshly prepared solutions and administer within one hour after preparation.

Vial Size Ampicillin/Sulbactam	Volume of Diluent to be Added	Withdrawable Volume*
500 mg/250 mg	1.6 ml	2.0 ml
1000 mg/500 mg	3.2 ml	4.0 ml
2000 mg/1000 mg	6.4 ml	8.0 ml

*There is sufficient excess present to allow withdrawal and administration of the stated volumes.

Preparation for Intravenous Use: Preparation of UNASYN sterile powder in piggyback units may be diluted directly to the desired concentrations using the diluents listed below.

Vials of UNASYN sterile powder may be initially reconstituted with sterile water for injection to yield solutions containing 250 mg ampicillin/125 mg sulbactam per ml (see Preparation for Intramuscular Use). An appropriate volume should then be immediately diluted to yield solutions containing from 2 to 30 mg ampicillin/and from 1 to 15 mg sulbactam per ml. The following parenteral diluents and approximate concentrations of UNASYN provide stable solutions for the time periods indicated in the table below. (After the indicated time periods, unused portions of solutions should be discarded.)

Permissible use periods in different diluents for intravenous infusion are:

Diluent	Maximum Concentration (mg/ml) Ampicillin/Sulbactam	Use Period
Sterile Water for Injection	30/15	8 hr @ 25°C
	30/15	48 hr @ 4°C
	20/10	72 hr @ 4°C
0.9% Sodium Chloride Injection	30/15	8 hr @ 25°C
	30/15	48 hr @ 4°C
	20/10	72 hr @ 4°C
5% Dextrose Injection	20/10	2 hr @ 25°C
	20/10	4 hr @ 4°C
	2/1	4 hr @ 25°C
Lactated Ringer's Injection	30/15	8 hr @ 25°C
	30/15	24 hr @ 4°C
M/6 Sodium Lactate Injection	30/15	8 hr @ 25°C
	30/15	8 hr @ 4°C
5% Dextrose in 0.45% Saline	[illegible]	4 hr @ 25°C
	10/5	4 hr @ 4°C
10% Invert Sugar	2/1	4 hr @ 25°C
	20/10	3 hr @ 4°C

Animal Pharmacology: While reversible glycogenosis was observed in laboratory animals, this phenomenon was dose- and time-dependent and is not expected to develop at the therapeutic doses and corresponding plasma levels attained during the relatively short periods of combined ampicillin/sulbactam therapy in man.

HOW SUPPLIED

UNASYN (ampicillin sodium/sulbactam sodium) is supplied as a sterile off-white dry powder in glass vials and piggyback bottles. The following packages are available:

Vials containing .75 g (NDC 0049-0012-83) equivalent of UNASYN
(.5 g ampicillin as the sodium salt plus .25 g sulbactam as the sodium salt)
Vials containing 1.5 g (NDC 0049-0013-83) equivalent UNASYN
(1 g ampicillin as the sodium salt plus .5 g sulbactam as the sodium salt)
Vials containing 3 g (NDC 0049-0014-83) equivalent of UNASYN
(2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt)
Bottles containing 1.5 g (NDC 0049-0022-83) equivalent of UNASYN
(1 g ampicillin as the sodium salt plus .5 g sulbactam as the sodium salt)
Bottles containing 3 g (NDC 0049-0023-83) equivalent of UNASYN
(2 g ampicillin as the sodium salt plus 1 g of sulbactam as the sodium salt)

ROERIG Pfizer

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE	[illegible]
NDA NUMBER	[illegible]
IND NUMBER	
TELECON/MEETING	
INITIATED BY: ☐ APPLICANT/SPONSOR ☐ FDA	MADE: ☐ BY TELEPHONE ☐ IN PERSON
PRODUCT NAME	[illegible]
FIRM NAME	[illegible]
NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD	Dr [illegible]
TELEPHONE NO.	203 [illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

of the [illegible]

[illegible]

[illegible]

[illegible] UK

[illegible]

[illegible]

[illegible]

[illegible]

Allergan [illegible]

[illegible]

[illegible]

[illegible]

cc M. [illegible]

[illegible]

[illegible]

SIGNATURE

[illegible]

DIVISION

[illegible]

FORM FD 2587 (11/77)

DIVISION FILE

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

Memorandum of Telephone Conversation
September 12, 1986

Between James Ramsey Ph.D
Microbiologist HFN 815

and Robert F. Myers, Ph.D.
Assistant Director
Drug Regulatory Affairs
Pfizer Inc.
Groton, Connecticut 06340

Re. Label for Unasyn, NDA 50-608

The labels submitted for approval did not indicate labeling for lot numbers and an expiration date. I asked Dr. Myers if the lot and expiration indications would be added when the numbers were to be printed on the label. He replied that all information indicating expiration date and lot numbers would be printed simultaneously when the labels were added to the vials. I told him that this was sufficient.

James Ramsey, Ph.D.
Microbiologist

NDA 50-608 April 29, 1986

Memorandum of Conference

Between: Pfizer:

D. J. Mehta, M.D. (Pfizer, CT)
A. K. Knirsch, M.D. (Pfizer, CT)
R. F. Myers, Ph.D. (Pfizer, CT)
H. Swang, M.D. (Pfizer, NY)
C. Bluestone, M.D. (Children's Hospital of Pittsburgh)

and: FDA-DAIDP:

E. Tabor, M.D.
C. Stanley, M.D.
M. Albuerne, M.D.
R. Norton
J. Ramsey, Ph.D.
K. Creedon

Subject: Inadequate data for epiglottitis claim and proposed method for changing the fixed ratio of drug combination (ampicillin and sulbactam, UNASYN).

Dr. Bluestone briefly described the previously and currently used therapy for pediatric patients with epiglottitis. He described the 6 patients with confirmed ampicillin-resistant, beta-lactamase producing Haemophilus influenzae whom he has treated with parenteral ampicillin and sulbactam, on which a 100 percent cure rate is based. Dr. Knirsch noted that a seventh patient had been treated since the results of the original 6 patients had been submitted and handed a desk copy of the seventh patient's case report forms to Dr. Albuerne.

Dr. Albuerne explained to the sponsor that this pediatric claim could not be granted based on only 6 patients in a single-controlled study without any supportive data from other pediatric indications.

Dr. Knirsch noted that there were two patients with resistant H. influenzae who were enrolled in the controlled meningitis study that demonstrated eradication of the pathogen. Drs. Tabor, Stanley and Albuerne all agreed that a total of 8 patients was still inadequate to put a claim for these indications into the package insert.

Various regions with a high incidence of resistant H. influenzae were noted and possible investigators were suggested to the sponsor for their consideration in planning additional studies.

It was further suggested that the sponsor market the product for treatment of adults and that the pediatric claim be submitted as a new NDA since it would consist of a different fixed ratio of sulbactam:ampicillin than the adult dosage this would be considered a classification 3,C drug.

Kathleen A. Creedon

cc:
NDA 50-608
HFN-815
HFN-815/MO/MAlbuerne
HFN-815/MICRO/JRamsey
HFN-815/CSO/KCreedon
4776b

DRUG CONTROL REVIEW NOTES - #

Form 5 # 50-608

Rx, OTC (type of drug) Rx

DOSAGE FORM: Injection

SPONSOR: Pfizer Inc.
Eastern Point Road

SUBMISSION REVIEWED:

a. Original dated: 4/19/85

b. Amendments dated: 4/14/86

c. Providing for:

NAMES:

a. TRADE: Unasyn

b. NON-PROPRIETARY: Ampicillin Sodium/Sulbactam Sodium

c. CHEMICAL:

d. ESTAB:

e. USAN:

f. WHO:

STRUCTURAL FORMULA:

RELATED NDA, IND, MF, FORM 5's:

REMARKS: Clinical data supporting efficacy against methicillin resistant Staphylococcus species are not sufficient. The package insert must have a statement that says that methicillin resistant Staphylococcus must be considered resistant to Unasyn regardless of zone diameter if the proposed chart is to be retained. Alternatively, Staphylococcus species must be listed separately from Enterobacteriaceae and show a zone diameter $\geq$ 20 mm for susceptible organisms.
(See enclosure 5, page 5).

James C. Ramsey

(Reviewer) James C. Ramsey
Microbiologist
HFN-815
5/12/86

cc: Orig. Form 5 # 50-608
HFN-815
HFN-815/CSO
HFN-178
HFN-235
HFN-815/JCRamsey/5/14/86/dh
R/D: init. by RNorton/5/ /86

MED REVIEW

NDA 50-608

December 19, 1986

Medical Officer's Review of Package Insert

Applicant: Pfizer Laboratories

Name of Drug: UNASYN

The revised copy of the package insert for UNASYN (ampicillin/sulbactam), dated December 19, 1986, appears adequate.

Mercedes S. Albuerne, M.D.

cc:
Orig NDA
HFN-815
HFN-815/CSO
HFN-340
HFN-815/MSAlbuerne:mas-12/19/86-0392d

NDA 50-60 July 7, 1986

Medical Officer's Review of Package Insert for UNASYN
(ampicillin sodium/Sulbactam sodium)

The proposed package insert for UNASYN (ampicillin sodium/sulbactam sodium), revised according with the recommendations provided by the DAIDP reviewing team, appears adequate.

There is, however, a typographical error on page 3, under "Microbiology", second paragraph, third sentence. The word "plasmid" has been spelled incorrectly. The Sponsor should be asked to correct this mistake.

Mercedes S. Albuerne, M.D.

cc:
Orig NDA
HFN-815
HFN-815/CSO
HFN-340
HFN-515/RNorton
HFN-815/MAlbuerne:js/7/7/86
1239

Preface
to
Medical Officer's Review of NDA 50-608

For the convenience of the reviewers, the most important studies which provided the evidence to support the recommendation to approve UNASYN (sulbactam/ampicillin) for the treatment of the conditions enumerated under "Overall Conclusions" of the MOR (page 1[illegible]0) are listed below:

<u>LOWER RESPIRATORY TRACT INFECTIONS</u>
<u>Open Studies</u>
Protocol # 52-1 (Pages 110-112) - 9 cases
Protocol # 52-2 (Pages 112-114) - 4 cases
Protocol # 77-1 (Pages 127-130) - 18 cases

<u>SKIN and SKIN STRUCTURE INFECTIONS</u>
<u>Controlled Study</u>
<u>Protocol A</u> (Pages 44-51)
Sulbactam/ampicillin - 21 cases
Clindamycin/aminoglycoside - 24 cases

<u>Open Studies</u>

Study # 02-1	(Pages 61-63)	-	16 cases
Study # 04-1	(Pages 63-65)	-	13 cases
Study # 20-1	(Pages 65-68)	-	66 cases
Study # 12-2	(Pages 68-70)	-	5 cases
Study # 35-1	(Pages 101-102)	-	10 cases

<u>URINARY TRACT INFECTIONS</u>
<u>Open studies</u>

Protocol # 28-2	(Pages 97-99)	-	14 cases
Protocol # 38-1	(Pages 102-104)	-	9 cases
Protocol # 54-1	(Pages 115-116)	-	11 cases
Protocol # 72-1	(Pages 120-122)	-	9 cases

<u>INTRA ABDOMINAL INFECTIONS</u>
<u>Controlled Studies</u>
<u>Protocol # 21-1</u> (Pages 35-39)
Sulbactam/ampicillin - 58 cases
Clindamycin/gentamicin - 35 cases

<u>Protocol B</u> (Pages 88-91)
Sulbactam/ampicillin - 11 cases
Metronidazole/gentamicin - 10 cases

Protocol # 29-3 (Pages 91-94)
Sulbactam/ampicillin - 24 cases
Clindamycin/gentamicin - 17 cases

Open Study
Protocol # 52-2 (Pages 112-114) - 8 cases

GYNECOLOGICAL INFECTIONS
Controlled Study
Protocol A (Pages 44-51)
Sulbactam/ampicillin - 9 cases
Clindamycin/aminoglycoside - 9 cases

OPEN STUDY
Protocol # 73-1 (Pages 122-123) - 9 cases

An overall summary of all clinical studies may be found on page 148.

Mercedes S. Albuerne, M.D.

cc:
Orig NDA
HFN-340
HFN-815
HFN-815/CSO
HFN-815/MSAlburne/jlm/4/3/86
0887m

NDA 50-608

Medical Officer's Review of NDA 50-608

M.O. Review #1

Applicant: Pfizer Central Research
Medical Research Laboratories
Groton, Connecticut

Date of Application: April 18, 1985

Date Review Started: May 6, 1985

Date Review Completed: December 16, 1985

1. General Information

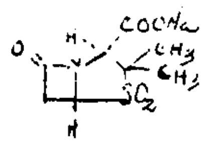
A) Name of Drug
(1) Generic: Sulbactam sodium and ampicillin sodium
(2) Trade: UNASYN
(3) Chemical:

Sulbactam sodium
Sodium (2S, 5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate 4,4-dioxide

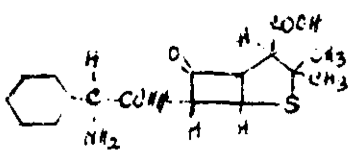
Ampicillin sodium
Monosodium (2S, 5R, 6R)-6-[(R)-2-amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate

Chemical Structure

Sulbactam sodium



Ampicillin sodium



B) Pharmacologic Category

Sulbactam is an irreversible inhibitor of several bacterial beta-lactamases. It is a derivative of the basic penicillin nucleus, but possesses little useful antibacterial activity except against the Neisseriaciae.

Ampicillin is a semi-synthetic penicillin with a broad spectrum of activity against penicillin-susceptible gram-positive organisms and several gram-negative pathogens. However, it does not resist destruction by beta-lactamases.

C) Proposed Indications
The proposed indications of Unasyn are the conditions listed below when caused by susceptible beta-lactamase producing gram-positive and gram-negative aerobic and anaerobic microorganisms.

1 - Upper respiratory tract infections
2 - Lower respiratory tract infections
3 - Skin and skin structure infections
4 - Urinary tract infections
5 - Intra-abdominal infections
6 - Gynecologic infections
7 - Bacterial septicemia
8 - Bone and joint infections
9 - CNS infections

D) Dosage Form
Unasyn, sulbactam sodium/ampicillin sodium parenteral combination, is available as a dry powder for reconstitution in vials containing the equivalent of 1000mg + 2000 mg, 500 mg + 1000 mg, 250 mg + 500 mg and 125 mg + 250 mg of sulbactam and ampicillin, respectively.

E) Route of Administration
Unasyn may be administered by either I.V. or I.M. routes.

2. Manufacturing Controls
(Refer to Chemistry Review)

3. Pharmacology
(Refer to Pharmacology Review)

Preclinical Studies

Microbiology

Study I.A. - In Vitro Antibacterial Spectrum of Sulbactam
The *in vitro* activity of sulbactam and ampicillin against a spectrum of gram-positive and gram-negative organisms is shown in Table 1 below.

Table 1

Primary In Vitro Activity of Sulbactam and Ampicillin

Organism	Strain No.	MIC (mcg/ml) Sulbactam	Ampicillin
S. aureus (S)	5	200	< 0.10
S. aureus (R)	400	200	200
S. epidermidis	111	50	≤ 0.10
S. pyogenes	203	50	< 0.10
S. faecalis	006	> 200	0.78
E. coli (R)	172	50	6.25
E. coli (R)	129	200	100
E. coli (S)	266	25	3.12
K. pneumoniae	009	50	12.5
K. pneumoniae	079	25	25
S. marcescens	001	100	12.5
E. cloacae	005	100	100
E. aerogenes	040	25	3.12
H. influenzae	012	100	0.78
P. aeruginosa	104	> 200	200
B. fragilis	-	25-50	200
N. gonorrhoeae	F18	0.15	0.07

S = Ampicillin susceptible
R = Ampicillin resistant

These results show that sulbactam *per se* has weak antibacterial activity compared to ampicillin. The potent activity of sulbactam against *N. gonorrhoeae* is an obvious exception.

Study I.B. - Activity of Sulbactam against N. gonorrhoeae
The activity of sulbactam against *N. gonorrhoeae* isolates is presented in Table 2.

Table 2

In Vitro Activity of Sulbactam, Ampicillin and Sulbactam/Ampicillin against N. gonorrhoeae

Strain No.	MIC (mcg/ml) Sulbactam	Ampicillin	Sulbactam/Ampicillin
F-18CDC	0.15	0.07	0.07/0.07
G-9	3.12	0.09	0.09/0.09
66001	0.31	0.02	0.02/0.02
66008	0.15	0.02	0.02/0.02
CDC(R)	1.2	>10	0.3 /0.3
CDC(R)	2.5	>10	0.9 /0.9

These data confirm that sulbactam is active against ampicillin susceptible and ampicillin resistant strains of *N. gonorrhoeae*. In addition, there is a synergistic response between sulbactam/ampicillin against the resistant isolates.

There is also a reference in the literature by Doern *et al* which presents data showing that sulbactam markedly lowered ampicillin MICs to *Branhamella (Neisseria) catarrhalis* strains harboring a beta-lactamase.

Study I.C. - Mode of Action of Sulbactam Against a Type III Beta-Lactamase.

The purpose of this study was to demonstrate that sulbactam is a non-competitive and irreversible beta-lactamase inhibitor. Beta-lactam hydrolysis was measured at 37°C in 0.05M potassium phosphate. Kinetic analyses were done with a Type III constitutive *E. coli* beta-lactamase (unpurified). Initial rates of hydrolysis were measured at various concentrations of penicillin G in the presence and absence of sulbactam.

The inhibition of the Type III constitutive *E. coli* cell-free beta-lactamase preparation by sulbactam is mechanistically complex. Penicillin G hydrolysis was inhibited initially in a competitive fashion, but within two minutes mixed inhibition kinetics were observed. Non-competitive (irreversible) inhibition was obtained by preincubating the enzyme with a low concentration of sulbactam for ten minutes at 37°C before the addition of penicillin G. The irreversibility of this inhibition was also tested in a second experiment. Here, the enzyme was almost completely inactivated by incubating with sulbactam for one hour. Next, the enzyme was dialyzed in order to remove excess inhibitor. This was completed within two hours, but at most, only 8% of the original beta-lactamase activity was regenerated. Thus, it is proposed that sulbactam first forms a reversible complex with the enzyme (competitive inhibition). This complex reacts to form an inactivated enzyme inhibitor complex, leading to non-competitive inhibition. This complex is stable (irreversible).

Interpretation: The competitive component of inhibition is important as this allows sulbactam to compete with the substrate, i.,e., gain access to the active site of the beta-lactamase molecule. The non-competitive inhibition effectively inactivates the enzyme long enough for the beta-lactam antibiotic, ampicillin, to react with the penicillin binding proteins responsible for cell wall biosynthesis.

Study I.D. - The Beta-Lactamase Inhibitory Spectrum of Sulbactam

Sulbactam is capable of inhibiting a variety of important beta-lactamases from hydrolyzing ampicillin and penicillin G, including the beta-lactamase from methicillin-resistant staphylococcal species.

Fu and Neu demonstrated that sulbactam is an effective inhibitor of the hydrolysis of penicillins and cephalosporins by both gram-positive and gram-negative Richmond type II, III and V beta-lactamase which are either plasmid or chromosomally mediated. Later they published a report on the beta-lactam-inactivating activity of *Legionella pneumophilia* to penicillins and cephalosporins. In the presence of sulbactam, the hydrolysis of beta-lactams was prevented. The enzyme in *L. pneumophilia* acted primarily as a cepholosporinase.

Study I.E. - Activity of Sulbactam in a 1:1 Combination with Ampicillin Against Beta-Lactamase Producing Organisms

Synergy (defined as at least a four-fold reduction in the MIC of both agents) of sulbactam in a 1:1 combination with ampicillin was demonstrated against the following beta-lactamase producing organisms: S. aureus 01A10 and 01A400, S. epidermidis 01B126, H. influenzae 54A036, K. pneumoniae 53A009 and 53A031, S. marcescens 63A017, P. stuartii 77A013, and M. morganii 97A001.
Synergy was not seen against E. coli 51A129, K. oxytoca 53D024, E. cloacae 67B009 and P. aeruginosa 52A104.

Study I.F. - In Vitro Antibacterial Activity of Sulbactam/Ampicillin Against 600 Bacterial Isolates

In an extensive in vitro study involving 616 ampicillin resistant clinical isolates, it was demonstrated that sulbactam is a potent inhibitor of the beta-lactamase found in a variety of gram-positive and gram-negative bacteria. Over 90% of the Staphylococcus, including methicillin-resistant S. aureus, Bacteroides, Haemophilus, Klebsiella, E. coli, E. aerogenes and Proteus species were inhibited by 16/16 mcg/ml of ampicillin/sulbactam.

Study I.G. - Activity of Sulbactam/Ampicillin Against Bacteroides fragilis

In this study, over 100 mcg/ml of ampicillin were required to inhibit 90% of the 51 B. fragilis strains tested. However, when 3.12 mcg/ml of sulbactam plus 6.25 mcg/ml of ampicillin were combined, 90% of the 51 strains were inhibited.

Study I.H. - Bactericidal Activity of the Sulbactam/Ampicillin Combination

Comparison of the bacteriostatic - bactericidal activity of a 1:1 combination of ampicillin/sulbactam against 28 ampicillin resistant strains of Staphylococcus aureus is presented in Table 3.

Table 3

% of Strains Inhibited	Values* in mcg/ml					
	Ampicillin		Sulbactam		Ampicillin/Sulbactam	
	MIC	MBC	MIC	MBC	MIC	MBC
50	100	200	200	>200	3.12	6.25
75	100	>200			6.25	12.5
90	200				6.25	50

Comparison of the bacteriostatic-bactericidal activity of a 1:1 combination of ampicillin/sulbactam against 17 ampicillin-resistant strains of H. influenzae is presented in Table 4.

Table 4

% of Strains Inhibited	Ampicillin MIC	Ampicillin MBC	Sulbactam MIC	Sulbactam MBC	Ampicillin/Sulbactam MIC	Ampicillin/Sulbactam MBC
	Values* in mcg/ml					
50	200	> 400	100	100	3.12	3.12
75	400		100	200	3.12	6.25
90	> 400		200	200	6.25	6.25

*Values represent total beta-lactam concentration, e.g., 3.12 mcg/ml equals 1.56 ampicillin plus 1.56 sulbactam.

As shown in Tables 3 and 4, the combination of sulbactam/ampicillin is bactericidal. MBCs against S. aureus were generally only one dilution higher than the MICs. Five of the 28 S. aureus strains were beta-lactam "tolerant" strains. These isolates possess a form of penicillin resistance that differs from resistance due to beta-lactamase and resistance due to intrinsic (e.g. methicillin resistance) mechanisms in that their MIC's are normal but their MBCs are generally high against cell wall active antibiotics (nafcillin). This explains the apparent lack of significant MBC activity at the 90 percent level and was not due to inactivity against a beta-lactamase.
Against H. influenzae, the 90 percent MBC level was within one dilution of MICs.

Study I.I - A Determination of the Rate at Which Sulbactam/Ampicillin Kills Ampicillin Resistant Staphylococcus aureus and Bacteroides fragilis

In this experiment the combination of 3.12 mcg/ml sulbactam plus 3.12 mcg/ml ampicillin killed 99.9% of S. aureus cells in 24 hours. The combination of 6.25 mcg/ml of sulbactam and 0.78 mcg/ml of ampicillin was bactericidal, but the reverse ratio was not. This indicates that a sufficient level of sulbactam is required for maintaining bactericidal activity.

The combination of 3.12 mcg/ml sulbactam and 3.12 mcg/ml penicillin G killed over 99.9% of the penicillin G resistant B. fragilis cells within six hours.

Study I.J. - Comparative Activity of Different Ratios of Sulbactam/Ampicillin Against Resistant Staphylococcus aureus

Sulbactam in combination with ampicillin at ratio of 1:1, 1:2, or 2:1 exhibits synergestic activity as shown in Table 5.

Table 5

Activity of Single Agents and Combinations Against 45 Resistant Staphylococcus aureus Isolates

A. Activity of Components

% of Isolates Inhibited	MIC (mcg/ml) of Single Agents Sulbactam	Ampicillin
50	200	50
75	200	200
90	200	200

B. Activity of Combinations

% of Isolates Inhibited	MIC (mcg/ml) at Ratio of Sulbactam: Ampicillin 1:1	2:1	1:2
50	1.56 + 1.56	1:56 + 0.78	0.78 + 1.56
75	3.12 + 3.12	3.12 + 1.56	1.56 + 3.12
90	3.12 + 3.12	6.25 + 3.12	3.12 + 6.25

Aswapokee and Neu reported that the combination of sulbactam and ampicillin was synergistic at ratios of ampicillin to sulbactam of 1:1, 5:1 and 10:1, although complete synergy (4-fold reduction in MIC of both agents) was shown for significantly fewer isolates at an ampicillin to sulbactam ratio of 10:1. In addition, Retsema et al reported that an ampicillin to sulbactam ratio of 4:1 (as well as a 1:1 and a 2:1 ratio) was highly synergistic against a battery of 21 methicillin-resistant staphylococci.

Study I.K. - Emergence of Resistance in the Presence of Sulbactam/Ampicillin

The emergence of resistance to sulbactam/ampicillin by ampicillin resistant strains of S. aureus, H. influenzae and B. fragilis was determined by Retsema et al.
Results showed that S. aureus strains highly resistant to ampicillin were susceptible to the sulbactam/ampicillin combination (MIC 3.12/3.12 mcg/ml). After six transfers in the presence of a sublethal concentration of the combination, the MICs increased only a single tube dilution to 6.25/6.25 mcg/ml for all the 16 strains tested. The MIC of sulbactam/ampicillin remained the same (6.25/6.25 mcg/ml) after seven tranfers of H. influenzae strains in the presence of sublethal amounts of the combination and increased only one dilution after seven transfers with B. fragilis strains highly resistant to ampicillin.
These results demonstrate that ampicillin resistant S. aureus, H. influenzae and B. fragilis strains do not readily develop resistance to the sulbactam/ampicillin combination.

Study I.L. - Protection of Ampicillin by Sulbactam Against Resistance Development

The MIC values of sulbactam, ampicillin and sulbactam/ampicillin (1:1) against mixed inocula composed of ampicillin resistant 01A400 and ampicillin susceptible 01A005 staphylococci were determined. S. aureus 01A005 was susceptible to ampicillin at an MIC of 0.19 mcg/ml. In contrast, the 01A400 strain required more than 100 mcg/ml of ampicillin to inhibit its growth. The presence of up to 10,000 resistant cells had a minimal effect on MIC values (0.39 to only 1.56 mcg/ml) for ampicillin. However, higher numbers of resistant cells in the mixture effectively destroyed the activity of ampicillin. In contrast the 1:1 mixture of the sulbactam/ampicillin was highly active against the controls and all mixed inocula.
Sulbactam per se was ineffective against all mixed populations at 100 mcg/ml.

To further challenge the sulbactam/ampicillin combination, a series of serial transfer studies starting with mixed resistant and susceptible staphylococci inocula were carried out. Cephalexin and cefaclor were included as control antibioties. The activity of ampicillin (without sulbactam) was lost after a single passage against inocula containing small numbers of the resistant S. aureus 01A400. By the fourth passage both cephalosporins exhibited significant increases in MIC values. Sulbactam/ampicillin MICs were also increased over the 10 passage series; however, the 6.25/6.25 mcg/ml concentrations observed at the end are well within achievable levels following parenteral administration of the combination.

Study I.M. - Studies on the Stability of Sulbactam at Different pH Values

The in vitro stability of sulbactam was evaluated at pH 2.6, pH 7.0 and pH 8.0 At the three pHs tested, sulbactam retained essentially full activity over an interval of 24 hours. Under these conditions, the half-life was greater than 100 hours.

English et al also demonstrated that sulbactam is stable in human serum at pH 7.4 and human urine at pH 9.0 for more than 100 hours. In human urine at pH 4.5 the estimated half-life is 82 hours.

Study I.N. - Other Studies Included in the Preclinical Development of Sulbactam/Ampicillin

Influence of Medium. - The activity of sulbactam/ampicillin has been evaluated against resistant S. aureus in three different media using both broth and agar preparations. In addition to the routinely used BHI, the studies included Muller-Hinton and Trypticase Soy.
Sulbactam/ampicillin had almost identical potency in all three media whether carried out in broth or agar. Occasionally higher MICs were recorded in BHI medium probably due to better growth of the S. aureus in this rich medium.

Serum Protein Binding - The protein binding of sulbactam in human serum was observed to be approximately 38%, compared with 28% for ampicillin.

Affinity of Sulbactam for PBPs - Sulbactam has been shown to bind preferentially to PBPs 1a and 2 of *E. coli* K-12, although its affinity for these proteins is much lower than that of conventional penicillin antibiotics
No other PBPs bound sulbactam to any significant degree.

Antagonism - At no time in the course of bacteriological studies was there evidence of an antagonistic response to the sulbactam/ampicillin combination.

Study II.A. - Acute Systemic Protection Tests with Sulbactam in Combination with Ampicillin

The activity of sulbactam/ampicillin against a spectrum of bacterial infections in mice has been determined. All pathogenic strains tested were beta-lactamse producers highly resistant to ampicillin.
The sulbactam/ampicillin combination was active against all the isolates. Especially noteworthy was the activity demonstrated against methicillin-resistant *S. aureus* isolates (01A137 and 01A133) and the mixed anaerobic infection (*Bacteroides fragilis* plus *Fusobacterium necrophorum*).

Study II.B. - The Activity of Sulbactam/Ampicillin Against Experimental Urinary Tract Infections

The efficacy of sulbactam/ampicillin against experimental urinary tract infections in rats caused by ampicillin resistant strains of *Escherichia coli* and *Proteus vulgaris* has been evaluated.
Against the resistant *E. coli* infection, a 3.7 log reduction in viable bacteria in the kidney was observed. This compared favorably with the response effected by cefaclor.
Against the resistant *P. vulgaris* infection, a 2.3 log reduction in viable bacteria was observed. This activity was quantitatively identical to the action of indanyl carbenicillin, the positive control used in these studies.
Ampicillin and sulbactam as single agents were, as expected, without significant activity.

Study II.C. - Efficacy of Sulbactam/Ampicillin Against Localized Infection Models in Mice

The activity of sulbactam/ampicillin in localized infection models that are related to clinical situations such as skin and soft tissue infections was studied. Ampicillin alone, dicloxacillin, cephalexin and cefaclor were used as comparative agents.

Three different ampicillin resistant strains of *S. aureus* of varying susceptibility were used to produce these infections.
Other than the expected poor performance of ampicillin, the two cephalosporins, dicloxacillin and sulbactam/ampicillin performed well against these difficult to treat infections. Dicloxacillin's performance was somewhat inferior against the methicillin resistant strain 01A 137.

In an experimental suture infection in mice caused by S. aureus 01A400, sulbactam/ampicillin and cephalexin were effective in reducing the infection by a 2-log count from that of the infected control and ampicillin.

Study II.C.1 - Efficacy of Sulbactam/Ampicillin Against Localized Infection Models in Mice

The oral and parenteral dosage forms of sulbactam/ampicillin were evaluated in an experimental thigh infection in mice produced by an ampicillin-resistant S. aureus 01A400. Five commercial beta-lactam antibiotics were included for comparison purposes.

The high dose (100 + 100 mg/kg) of the oral (ampicillin/sulbactam pivoxil) and parenteral (ampicillin/sulbactam) dosage forms reduced the viable count of staphylococci in the thigh muscle by nearly five logs from that in the untreated controls. At the lower dosage studied (50+50 mg/kg), the parenteral dosage from reduced the viable count by four logs from that of the infected controls; the oral dosage form, by three logs.
This activity compared very favorably with that of cefazolin, oxacillin and methicillin. The activity of sulbactam/ampicillin was greater than that of dicloxacillin and cefalexin.

Cardiovascular Effects

Sulbactam/ampicillin was administered by 15 minute infusion to each of 4 anesthetized beagle dogs at a dose of 67 mg/kg of sulbactam and 133 mg/kg of ampicillin. After a 10 minute interval, sulbactam/ampicillin was administered by infusion to the same dogs at a dose of 134 mg/kg sulbactam/266 mg/kg ampicillin. No significant changes in mean blood pressure, heart rate or pattern of electrocardiogram were noted in any of the animals.
Blood samples were drawn from each animal before and after each infusion for determination of drug concentration. One minute after the end of the second infusion, the serum concentration of sulbactam ranged from 641 to 787 mcg/ml and that of ampicillin from 711 to 1507 mcg/ml.
Results of this study suggest that it is unlikely that sulbactam/ampicillin will have cardiovascular adverse effects in man.

Protein Binding

Protein binding of sulbactam, ampicillin and carbenicillin was determined in human, dog and mouse sera.
Approximately 38% of the sulbactam was bound to human serum protein. Ampicillin and carbenicillin were bound approximately 28% and 48%, respectively.
In dog serum, approximately 50% of the sulbactam, 18% of the Ampicillin and 33% of the carbenicillin were protein bound.
In mouse serum, 33% of the sulbactam and 27% of the ampicillin were protein bound. In the extravascular fluid from the mouse, 20% of the sulbactam and 16% of the ampicillin were protein bound.

Pharmacokinetic Studies

Study #07-2

Title: The Kinetics of Intravenous and Intramuscular Ampicillin/Sulbactam in Man

Investigator: Donald J. Weidler, M.D., Division of Clinical Pharmacology, University of Miami

Procedure: Sixteen volunteers received 1.0 g ampicillin/0.5 g sulbactam by 15 minute infusion and by I.M. injection in a cross-over pattern. Eight other volunteers received a 15 minute infusion of 2.0 g ampicillin/1.0 g sulbactam, and an additional eight subjects received a single I.M. injection of 0.5 g ampicillin/0.25 g sulbactam. Serum and urine samples were obtained and assayed for sulbactam and ampicillin.

Results:

Mean Serum Concentrations of Sulbactam (16 subjects)
Dose = 15 minute infusion of 1.0 g ampicillin/0.5 g sulbactam

Concentration (mcg/ml)										
Time (hours)										AUC
0.10	0.25	0.50	0.75	1.00	1.50	2.00	4.00	6.00	8.00	(Hrs. mcg/ml)
29.67	21.48	15.31	11.42	9.06	5.75	3.90	1.04	0.39	0.12	32.54

Mean Serum Concentration of Ampicillin (16 subjects)
Dose = 15 minute infusion of 1.0 g ampicillin/0.5 g sulbactam

Concentration (mcg/ml)										
Time (hours)										AUC
0.10	0.25	0.50	0.75	1.00	1.50	2.00	4.00	6.00	8.00	(Hrs. mcg/ml)
57.51	38.93	28.49	19.26	14.35	8.52	5.91	1.45	0.42	0.16	55.03

Mean Urinary Recovery of Sulbactam and Ampicillin (16 subjects)
Dose = 15 minute infusion of 1.0 g ampicillin/0.5g sulbactam

Sulbactam Concentration (mcg/ml)

0-4 Hours	4-8 Hours	Total Recovery (% of dose)
981	43.6	86.0

•Ampicillin Concentration (mcg/ml)

0-4 Hours	4-8 Hours	Total Recovery (% of dose)
2100	68.7	86.4

Mean Serum Concentrations of Sulbactam and Ampicillin(16 subjects)
Dose = I.M. injection of 1.0 g ampicillin/0.5 g sulbactam

Sulbactam Concentration (mcg/ml)

Time (hours)										AUC
0.10	0.25	0.50	0.75	1.00	1.50	2.00	4.00	6.00	8.00	(Hrs. mcg/ml)
4.15	8.18	11.3	12.26	11.72	10.15	8.11	2.79	1.07	0.42	35.72

Ampicillin Concentration (mcg/ml)

Time (hours)										AUC
0.10	0.25	0.50	0.75	1.00	1.50	2.00	4.00	6.00	8.00	(Hrs. mcg/ml)
5.40	10.38	15.56	16.97	16.59	15.43	13.48	4.53	1.33	0.58	53.98

Mean Urinary Recovery of Sulbactam and Ampicillin (16 subjects)
Dose = I.M. injection of 1.0 g ampicillin/0.5 g sulbactam
Sulbactam Concentration (mcg/ml)

0-4 Hours	4-8 Hours	Total Recovery (% of dose)
1005	122	82.2

Ampicillin Concentration (mcg/ml)

0-4 Hours	4-8 Hours	Total Recovery (% of dose)
1724	234	73.8

Mean Serum Concentrations of Sulbactam and Ampicillin(8 subjects)
Dose = I.M. injection of 2 g ampicillin/1 g sulbactam

Sulbactam Concentration (mcg/ml)

Time (hours)										AUC
0.10	0.25	0.50	0.75	1.00	1.50	2.00	4.00	6.00	8.00	(Hrs. mcg/ml)
68.01	50.80	37.27	26.43	20.69	12.34	8.83	2.04	0.71	0.29	73.61

Ampicillin Concentration (mcg/ml)

Time (hours)										AUC
0.10	0.25	0.50	0.75	1.00	1.50	2.00	4.00	6.00	8.00	(Hrs. mcg/ml)
124.2	94.51	65.32	45.75	32.99	18.19	11.5	2.97	1.05	0.35	121.96

Mean Urinary Recovery of Sulbactam and Ampicillin(8 subjects)
Dose = 15 minute infusion of 2 g ampicillin/1 g sulbactam

Sulbactam Concentration (mcg/ml)

0-4 Hours	4-8 Hours	Total Recovery (% of dose)
1478	35.2	80.0

Ampicillin Concentration (mcg/ml)

0-4 Hours	4-8 Hours	Total Recovery (% of dose)
2921	93.1	78.1

Mean Serum Concentration of Sulbactam and Ampicillin (8 subjects)
Dose = I.M. injection of 0.5 g ampicillin/0.25 g sulbactam

Sulbactam Concentration (mcg/ml)

Time (hours)										AUC
0.10	0.25	0.50	0.75	1.00	1.50	2.00	4.00	6.00	8.00	(Hrs. mcg/ml)
2.79	6.13	6.99	6.84	6.10	4.74	3.21	0.87	0.28	0.08	16.09

Ampicillin Concentration (mcg/ml)

Time (hours)										AUC
0.10	0.25	0.50	0.75	1.00	1.50	2.00	4.00	6.00	8.00	(Hrs. mcg/ml)
4.83	9.23	12.34	11.91	11.85	8.90	6.21	1.58	0.45	0.16	29.39

Mean Urinary Recovery of Sulbactam and Ampicillin(8 subjects)
Dose = I.M. injection of 0.5 g ampicillin/0.25 g sulbactam

Sulbactam Concentration (mcg/ml)

0-4 Hours	4-8 Hours	Total Recovery (% of dose)
425	32.2	79.4

Ampicillin Concentration (mcg/ml)

0-4 Hours	4-8 Hours	Total Recovery (% of dose)
986	87.5	92.3

Mean Serum Half-Life (T 1/2) of Sulbactam and Ampicillin

		Half-Life (hours)	
Dose	Route	Sulbactam	Ampicillin
2 g ampicillin/1 g sulbactam	I.V.	1.02	1.02
1 g ampicillin/0.5 g sulbactam	I.V.	1.08	0.98
1 g ampicillin/0.5 g sulbactam	I.M.	1.32	1.22
0.5 g ampicillin/0.25 g sulbactam	I.M.	1.12	1.03

Renal and Non-renal Clearances of Ampicillin and Sulbactam in Normal Subjects

Route	Dose(g)	Clearance (ml/min) Renal	Non-Renal	Total
Sulbactam				
I.V.	1.0	177	52	229
I.V.	0.5	208	60	269
I.M	0.5	203	40	241
I.M	0.25	207	51	258
ALL	ALL	201	50	251
Ampicillin				
I.V.	2.0	215	59	274
I.V.	1.0	259	59	315
I.M.	1.0	248	75	324
I.M.	0.5	266	28	282
ALL	ALL	249	59	306

The mean peak serum concentrations following the fifteen minute infusion of 2 g ampicillin/ 1 g sulbactam were 124 mcg/ml ampicillin and 68 mcg/ml sulbactam. One gram ampicillin/0.5 g sulbactam (I.V.) produced peak concentrations of 58 mcg/ml ampicillin and 30 mcg/ml sulbactam. I.M. doses of 1 g ampicillin/0.5 g sulbactam produced peak serum concentrations of 18 mcg/ml ampicillin and 13 mcg/ml sulbactam. Urinary recoveries following I.V. and I.M. doses were similar for both drugs. Total clearance was approximately 306 ml/min for ampicillin and 251 ml/min for sulbactam. Renal clearance was 249 ml/min for ampicillin and 201 ml/min for sulbactam.

Following I.V. administration, the distribution of ampicillin and sulbactam was moderately rapid with half-lives of 42 minutes for sulbactam and 66 minutes for ampicillin. The apparent volume of distribution for the central compartment (blood and rapidly equilibrating tissues) was 146 for sulbactam and 154 ml/kg for ampicillin. The whole body volume of distribution (for I.V. doses) was 384 ml/kg for ampicillin and 332 ml/kg for sulbactam.

Study #01-3: The Kinetic Interaction of Sulbactam with Ampicillin or Penicillin G in Man

Investigator: Sherrard L. Hayes, M.D., Department of Pharmacology, University of Miami.

Procedure: This was a three-way cross-over study of sulbactam, ampicillin, and penicillin G, alone and in combination. Six patients were used for each of three dosing regimens: 1) 500 mg sulbactam and 500 mg penicillin G, alone and in combination, I.V. infusion for 30 minutes; 2) 500 mg sulbactam and 500 mg penicillin G, alone and in combination, I.M. injection; 3) 500 mg sulbactam and 500 mg ampicillin, alone and in combination, I.V. bolus. Comparisons were made for AUCs, peak concentrations of drug in serum, terminal half-lives and the percent recovered in urine for each drug administered alone vs. in combination.

Results:

Drug(a)	Route	Mean Value (N=6) AUC(b) (mcg.hr/ml)	Cmax(c) (mcg/ml)	t 1/2 (hrs)	Urinary Recovery (% of dose)
SUL(alone)	30 min I.V.	34.4	23.3	1.20	72.9
SUL(+PG)		36.0	28.4	1.30	77.8
PG(+SUL)		30.9	37.4	0.85	80.8
PG(alone)		25.8	27.7	0.87	86.1
SUL(alone)	I.M.	35.5	14.2	1.51	76.5
SUL(+PG)		43.1	12.1	2.47	97.4
PG(+SUL)		24.3	7.8	1.90	76.9
PG(alone)		30.4	7.7	1.87	68.1
SUL(alone)	I.V. Bolus	29.6	31.8	1.25	109.5
SUL(+AMP)		36.6	30.4	1.41	89.2
AMP(+SUL)		24.7	23.2	0.99	59.9
AMP(alone)		30.3	27.6	1.06	64.2

(a) SUL = sulbactam; PG = penicillin G; AMP = ampicillin
(b) penicillin G results are in u. hr/ml
(c) penicillin G results are in u/ml

Sulbactam had no consistent significant effect on the disposition of ampicillin or penicillin G. Additionally, the co-administration of ampicillin or penicillin G appeared to have no effect on the kinetics of sulbactam.

Study #07-3
Title: Phase I Bioequivalency Study of Sulbactam Sodium/Ampicillin Administered Intravenously to Normal Volunteers.

Investigator: Donald J. Weidler, Division of Clinical Pharmacology, University of Miami.

Study Design:
Single dose crossover study designed to establish serum levels, urinary excretion and bioequivalency following intravenous infusion of a fixed combination of 2 g ampicillin/1 g sulbactam compared to the same drugs reconstituted separately, then given together.

Procedure:
Sixteen healthy male volunteers were divided into two groups of eight subjects each. Group I was administered a fixed combination of 2 g ampicillin/1 g sulbactam by 15-minute intravenous infusion. Group II was given 2 g ampicillin and 1 g sulbactam that had been reconstituted separately then administered together by 15-minute IV infusion.
Group I and Group II reversed their drug assignments following a minimum 2-day washout period.

Results:

DOSE FORM	AUC (0-INF)	SULBACTAM Peak Max (mcg/ml)	Half-Life (1-6 hrs)	Recovered in Urine (%)
FIXED COMBINATION	63	55	1.06	77
SEPARATE RECONSTITUTION	64	58	1.03	75

DOSE FORM	AUC (0-INF)	AMPICILLIN Peak Max (mcg/ml)	Half-Life (1-6 hrs)	Recovered in Urine (%)
FIXED COMBINATION	126	125	1.03	84
SEPARATE RECONSTITUTION	119	119	1.00	79

The fixed combination of 2 g ampicillin/1 g sulbactam and the separately reconstituted 2 g ampicillin given with 1 g sulbactam are bioequivalent as indicated by similar AUCs, peak concentrations, half-life and urine recoveries.

Study #20-1
Title: A Comparison of the Pharmacokinetics, Toleratic and Safety of Sulbactam and Ampicillin after Administration of Single Intramuscular Doses Alone or in Combination.

Investigator: R. Mesure, M.D., Clinique St. Remi, Brussels, Belgium

Study Design: A 3-period crossover study in which each of 12 healthy young men received either 0.5 g sulbactam plus 0.5 g ampicillin, 0.5 g sulbactam alone or 0.5 g ampicillin alone as a single intramuscular injection. There were intervals of 7 days between each injection, and the allocation of treatment order was according to a computer-generated randomization list.
Samples of blood and urine were collected at various time intervals for drug assay.

Summary of Sulbactam and Ampicillin Pharmacokinetics

Treatment	Pharmacokinetic Parameter* Peak Conc. (mg/L)	AUC mg/L. hrs)	T 1/2 (hrs)	Median time to peak (hrs)
Sulbactam (0.5 g)	22.0	39.2	1.04	0.5
Sulbactam (0.5 g plus 0.5 g ampicillin	23.2	42.3	1.05	0.5
Ampicillin (0.5 g)	8.0	14.8	1.11	0.5
Ampicillin (0.5 g plus 0.5 g sulbactam	7.1	14.8	1.17	0.5

*Mean of values for 12 subjects

Summary of Sulbactam and Ampicillin Urinary Excretion

Urine Collection Period	Sulbactam levels following: 0.5 g sulbactam Amount (mg)	0.5 g sulb + 0.5g amp Amount (mg)	Ampicillin levels following: 0.5 g Ampicillin Amount (mg)	0.5 g amp + 0.5 g sulb Amount (mg)
0-24 hrs	447.4	412.5	288.0	287.6
% of dose	89.5	82.5	57.6	57.5

There were no significant differences in the peak plasma concentrations, AUCs, time to peak, plasma half-lives or urinary excretion of either drug when administration alone was compared with administration of the drugs in combination.

The only side effect relating to treatment was pain at the injection site which was experienced by most of the volunteers after each injection.

Study #24-2: The Pharmacokinetics, Toleration and Safety of Sulbactam After Intramuscular Administration Alone and Concomitantly with Oral Probenecid.

Investigator: R. Mesure, M.D., Clinique St. Remi, Brussels, Belgium

Design and Procedure: This was a four-period crossover study in which each of 12 adult volunteers received either 0.5 g or 1.0 g sulbactam as a single intramuscular injection in 1% lignocaine solution. On separate occasions each volunteer received the two doses of sulbactam alone and 30 minutes after taking 1.0 g probenecid orally. There was a minimum of 3 days between each injection and allocation of treatment order was according to a computer-generated randomization list.

Results:

Summary of Sulbactam Pharmacokinetic Parameters

Treatment	Peak Conc (mg/l)	t 1/2 (hrs)	AUC (mg/l.hr)	Vd (L)	Time to Peak (hrs)
0.5 g sulbactam	18.0	1.09	34.3	23.4	0.5 - 1
0.5 g sulbactam plus probenecid	20.8	1.43	49.1	22.3	0.5 - 1
1.0 g sulbactam	36.6	1.11	75.3	21.7	0.5 - 1
1.0 g sulbactam plus probenecid	36.1	1.51	92.2	24.2	0.5 - 1

Effect of Probenecid on Sulbactam Clearance

Treatment	Mean Sulbactam Clearance (ml/min)	Mean Creatinine Clearance (ml/min)
0.5 g sulbactam	255	183
0.5 g sulbactam after probenecid	183	181
1.0 g sulbactam	227	170
1.0 g sulbactam after probenecid	188	161

Mean Sulbactam Urine Levels

Urine Collection Period	0.5 g Sulbactam Amount (mg)	0.5 g Sulbactam after Probenecid Amount (mg)	1.0 g Sulbactam Amount (mg)	1.0 g Sulbactam after Probenecid Amount (mg)
0-3 hrs	350.5	315.6	657.3	626.4
3-6 hrs	70.1	81.5	177.4	176.7
6-12 hrs	11.3	24.2	27.8	63.4
12-24 hrs	1.1	2.2	2.9	3.5
Total 0-24 hrs	433.0	432.5	865.4	870.0
% of Dose	86.6	84.7	86.5	87.0

The concomitant administration of probenecid had little or no effect on the peak sulbactam concentration at either dose level, but in both cases elimination was delayed. This is reflected in the longer half-lives (t 1/2) and increased areas under the serum concentration/time curves (AUCs). The peak concentrations of sulbactam in serum and the AUCs were clearly proportional to the two dose levels given. The volume of distribution (Vd) of sulbactam was not affected by the presence of probenecid.
The sulbactam clearance was greater than the creatinine clearance when administered alone at both dose levels. The effect of concomitant dosing with oral probenecid was to reduce the sulbactam clearance to a value

close to that of creatinine. This strongly suggests that tubular secretion contributed to the renal clearance of sulbactam and that it was effectively inhibited by the oral administration of 1.0 g of probenecid. The proportion of the sulbactam dose detected in the urine collected in the 24-hour period after dosing was constant (84-87%), irrespective of the sulbactam dose level and whether or not there was concomitant treatment with oral probenecid. As expected, the urinary concentrations of sulbactam, were dose-related throughout the collection period. The delaying effect of probenecid on sulbactam clearance is most clearly apparent in the enhanced levels excreted during the 6-12 hour collection period as a consequence of the slightly reduced levels excreted during the 0-3 hour period.

Side Effects
Pain at the injection site was effectively controlled at the time of injection by the presence of 1% lignocaine in the injection solution, since only one volunteer reported mild pain. Inspection of the injection site after 24 hours revealed mild sensitivity to pressure on 10 occasions in a total of 6 volunteers. Five other side effects were experienced by 7 volunteers. There were 4 episodes of diarrhea and one instance each of dizziness, vomiting, itching and headache. Their association with the study treatment was considered uncertain by the investigator.

Transient small increases in laboratory test values were observed for ALT (1 subject), urea (3 subjects) and total bilirubin (1 subject). Because they had no dose relationship, and often were seen at baseline, they were not considered associated with treatment.

Study #81-2
Title: A Comparative Study of the Pharmacokinetics and Toleration of Sulbactam and Ampicillin after Intramuscular Administration of a Fixed Ratio Combination formulation (1:2, Sulbactam: Ampicillin) with and without Lignocaine

Investigators: R. Mesure, M.D. and J. de Palol, M.D., Clinique St. Remi, Brussels, Belgium

Study Design: A three-period crossover study in which eleven healthy young men received either 0.5 g sulbactam plus 1.0 g ampicillin in water, 0.5 g sulbactam plus 1.0 g ampicillin in 0.5% lignocaine solution or 0.25 g sulbactam plus 0.5 g ampicillin in 0.5% lignocaine solution as a single intramuscular injection. The injection volume was constant at 5 ml. There was a minimum of three days between each treatment, and the allocation of treatment order was according to a computer-generated randomization list.
Samples of blood and urine were collected at various time intervals for drug assay.

Summary of Sulbactam Serum Pharmacokinetics With and Without Lignocaine

Treatment	Pharmacokinetic Parameter: Peak Conc. (mg/L)	AUC (mg/L.hr)	T 1/2 (hrs)	Mean time to peak (hrs)
Sulbactam (0.5g)+ Ampicillin (1.0g) in water	10.8	21.5	1.2	0.75 (range 0.5 - 1.0)
Sulbactam (0.5 g)+ Ampicillin (1.0 g) in lignocaine	11.3	24.3	1.1	0.75 (range 0.5 - 1.5)
Sulbactam (0.25 g)+ Ampicillin (0.5 g) in lignocaine	6.4	9.9	1.0	0.5 (range 0.25 - 1.0)

Summary of Ampicillin Serum Pharmacokinetics With and Without Lignocaine

Treatment	Pharmacokinetic Parameter: Peak Conc. (mg/L)	AUC (mg/L.hr)	T 1/2 (hrs)	Mean time to peak (hrs)
Ampicillin (1.0g)+ Sulbactam (0.5g) in water	15.2	34.3	1.6	1.0 (range 0.5 - 2.0)
Ampicillin (1.0 g)+ Sulbactam (0.5 g) in lignocaine	15.7	36.0	1.3	0.75 (range 0.5 - 1.5)
Ampicillin (0.5 g)+ Sulbactam (0.25 g) in lignocaine	9.7	19.6	1.3	0.75 (range 0.5 - 1.0)

Summary of Sulbactam Urinary Excretion

Urine Collection Period	Mean Sulbactam Urinary Levels Following: 0.5 g Sulb + 1.0 g Amp in water	0.5 g Sulb + 1.0 Amp in lignocaine	0.25 g Sulb + 0.5 Amp in lignocaine
0-24 hrs(mg)	268	263	137
% of dose	53.6	52.6	54.8

Summary of Ampicillin Urinary Pharmacokinetics

Urine Collection Period	Mean Ampicillin Urinary Levels Following: 1.0 g Amp + 0.5 g Sulb in water	1.0 g Amp + 0.5 Sulb in lignocaine	0.5 g Amp + 0.25 Sulb in lignocaine
0-24 hrs(mg)	698	700	382
% of dose	69.8	70.0	76.4

No significant differences in peak serum concentration, AUC, serum half-life or urinary excretion were detected for either sulbactam or ampicillin when administration of 0.5 g sulbactam plus 1.0 g ampicillin, with and without lignocaine, was compared. There were the expected reductions in peak serum concentration and AUC for both drugs when the dose level of the combination was halved.

Tolerance
The only side effect related to treatment was pain at the injection site. All eleven volunteers rated the pain as severe or very severe when the dose of sulbactam: ampicillin (0.5: 1g) in water was administered. The median pain score was reduced to 1 (mild) when the dose was administered in the presence of 0.5% lignocaine.
Injection of half of this dose of sulbactam: ampicillin (0.25 g: 0.5 g) with 0.5% lignocaine was virturally painless, with only one volunteer reporting mild pain at the injection site.
Tenderness of the injection site was assessed 24 hours after each injection. The incidence decreased from 7/11 volunteers after injection of sulbactam plus ampicillin alone to 3/11 after both injections containing lignocaine.

Laboratory Test Results
Elevated serum CPK levels, accompanied by small elevations in serum AST levels in 5 volunteers, were detected after each injection in all eleven subjects. These were not affected by the presence of lignocaine in the injection solution.
Serum ALT levels were slightly elevated in one volunteer at the end of the study.
These laboratory test abnormalities are indicative of some degree of muscle damage and are consistent with the intramuscular injection site pain observed.

Study #64-1: A Pharmacokinetic Study of Sulbactam and Ampicillin Administered Concomitantly by Arterial Infusion in Newborn Infants

Investigator: Professor F. Cockburn, M.D., FRCP and Dr. T.A. McAllister, Royal Hospital for Sick Children, Yorkhill, Glasgow

Procedure: This pharmacokinetic study of sulbactam plus ampicillin was carried out in 16 newborn infants, 15 of whom were born prematurely. Each infant received either a single dose (6 infants) or multiple doses (10 infants) 12-hourly for up to 4 days of sulbactam plus ampicillin. Dosages were adjusted for body weight and were either 30 mg/kg of each drug (5 subjects) or 50 mg/kg of each drug (11 subjects) given by rapid infusion via an umbilical arterial catheter.

Results:
Mean elimination half-lives were 7.9 hours for sulbactam and 9.4 hours for ampicillin, probably reflecting the reduced renal function during the first few days of life.
Peak plasma concentrations of up to 330 mg/L were recorded for sulbactam and up to 320 mg/L were recorded for ampicillin after the 50 mg/kg dose. Substantial concentrations of both drugs, 6.8 - 110 mg/L of sulbactam and 4.8-160 mg/L of ampicillin were still present 12 hours after dosing. Urinary exretion was very variable, ranging from 7-91% of the administered dose for sulbactam and 5-132% for ampicillin.

Study #24-4
Title: Comparative Pharmacokinetics and Tissue Penetration of Sulbactam and Ampicillin after Concurrent Intravenous Administration

Investigator: Dr. R. Wise, Department of Medical Microbiology, Dudley Road Hospital, Birmingham, U.K.

Study Design:
An open, single-dose study in which six healthy male volunteers received a combination of 500 mg each of sulbactam and ampicillin intravenously, and subsequent serum, urine and blister (cantharides-induced) fluid levels were measured.

Results:
The mean serum levels of the compounds 30 minutes after dosing were approximately 20 mcg/ml for sulbactam and 14 mcg/ml for ampicillin. Generally, the serum levels of sulbactam were 1.5 times those of ampicillin.
Blister fluid levels were determined in five subjects, since one failed to produce adequate blisters. Peak concentrations of sulbactam and ampicillin were 19.2 mcg/ml and 8.1 mcg/ml, respectively. The sulbactam levels were approximately equal in serum and blister fluid at 0.5 hrs. The ampicillin levels in serum and blister fluid were approximately equal at 1.0 hr. The rate of elimination of both drugs from blister fluid was similar to that from serum.
The mean value of the initial concentration of sulbactam in serum was almost twice as high as that of ampicillin. Higher values of AUC were obtained for sulbactam than ampicillin; their mean values were 43.7 and 28.4 mcg/ml.hr, respectively.
Sulbactam and ampicillin had a similar serum half-life during the elimination phase; 0.99 and 1.04 hrs, respectively.
Approximately 85% of both drugs was excreted in the urine by 24 hours.

There were no side effects or laboratory test abnormalities in any of the volunteers.

Study 37-2: A Pharmacokinetic Study to Determine the Penetration of Sulbactam and Ampicillin into the Cerebrospinal Fluid of Patients with Meningitis

Investigator: Professor M. Micoud, M.D., Clinique de Maladies Infectieuses, Grenoble, France

Procedure:
Eighteen patients with meningitis participated in this pharmacokinetic study.
Sulbactam concentrations were determined in the CSF and serum of 6 meningitis patients 1.5 to 7 hours after administration of a single 1.0 g bolus injection and in 12 patients 1 to 7 hours after dosing, during the course of a regular multiple intravenous dosing regimen, with sulbactam (1.0 g). All patients were receiving an appropriate therapeutic course of ampicillin at doses ranging from 0.8 g to 2.0 g.

Results:
Sulbactam concentrations in the CSF varied widely between <0.15 - 12 mg/L, the degree of meningeal inflamation and the time after dosing being the principal factors affecting them. Penetration into the CSF occurred within 1 hour after dosing but did not persist as long as 7 hours in two patients sampled at these times. There was no clear difference in the concentrations achieved in the CSF when single and multiple dose regimen data were compared.

Ampicillin concentrations in the CSF were also very variable and, on the average were about double those of sulbactam, reflecting the higher dose levels used and the greater frequency of administration.
Antibacterially significant concentrations of both drugs were detected in the CSF in all patients except three, two who were not sampled until 7 hours after dosing and one in whom there was minimal evidence of meningeal inflamation.

Study #58-2
Title: Determination of Drug Concentrations in Peritoneal Fluid after a Single Intravenous Injection of Sulbactam Plus Ampicillin

Investigators: Dr. E. Houang and Mr. M. Chapman, Chelsea Hospital for Women, London

Procedure: Sixteen female subjects undergoing elective laparotomy were included in this study. Each subject received a single dose of sulbactam (500 mg) plus ampicillin (500 mg) by slow intravenous injection over 3 minutes given 0.5-2 hours prior to specimen collection at operation. Data from the 11 subjects from whom peritoneal fluid was obtainable were grouped together, corresponding with sampling times of approximately 0.5, 1, 1.5, and 2 hours post dosing.

Results: Both sulbactam and ampicillin distributed rapidly into the peritoneal fluid with the highest concentrations (means 14.5 and 7.1 mg/L, respectively) being detected at about 0.5 hours after dosing. The mean serum concentrations of sulbactam and ampicillin were 24.3 and 18 mg/L, respectively, at this time. The levels of both drugs in the peritoneal fluid appeared to decrease only slowly with time, and the mean concentrations at 2 hours post dosing were 10.9 mg/L for sulbactam and 7 mg/L for ampicillin. The corresponding concentrations in serum at this time were lower for both drugs (6.4 mg/L for sulbactam and 6.0 mg/L for ampicillin.

Study #60-2
Title: The Penetration of Sulbactam and Ampicillin into Peritoneal Fluid after Intravenous Administration

Investigators: Mr. I.A. Donovan, FRCS and Dr. R. Wise, M.D., MRCPath, Dudley Road Hospital, Birmingham, U.K.

Study Design:
This was an open, single-dose pharmacokinetic study in which 25 subjects undergoing elective intra-abdominal surgery volunteered to participate.

Eighteen patients received 1 g of sulbactam plus 1 g of ampicillin; seven patients received 1 g of sulbactam plus 2 g of ampicillin coadministered in sterile water as a bolus intravenous injection over 4 to 5 minutes at various times before the operation.

Results: Sulbactam and ampicillin penetrated the peritoneal fluid rapidly, with levels comparable to those found in serum as early as 7 minutes post-administration.
The level of sulbactam in the peritoneal fluid declined to 10 mcg/ml at 2.75 hrs. A level of ampicillin greater than 10 mcg/ml was found for 1.75 hours (after 1 g) and for 2.6 hours (after 2 g).

In the post distribution phase, the serum half-life of ampicillin (1 g) was 0.8 h and 0.97 h for sulbactam. The half-lives of the two agents in peritoneal fluid were 0.83 h for 1 g of ampicillin and 0.76 h for 1 g of sulbactam.
After a 1 g dose of each drug, the serum levels of sulbactam were 34% greater than those of ampicillin, and the peritoneal levels of sulbactam were 47 and 54% greater than those of ampicillin at 1.5 and 3 h, respectively.

After the 2 g dose of ampicillin, the serum levels were 3.05 times greater, and the peritoneal levels were 2.45 times greater than after 1 g, suggesting that twice the dose was accompanied by an approximately similar rise in serum and peritoneal levels.
The half-lives of ampicillin after the 2 g dose were 0.6 and 0.71 in serum and peritoneal fluid, respectively.
The mean percentage peritoneal penetration of sulbactam was 96% and of ampicillin was 92% for both dosage ratios.

Study 61-1: A Pharmacokinetic Study of Sulbactam (500 mg) Plus Ampicillin (500 mg) in Patients Undergoing Peritoneal Dialysis

Investigator: Dr. R. Gokal, Manchester Royal Infirmary, Manchester

Concentrations of sulbactam and ampicillin were monitored in the dialysate and serum of four patients with chronic renal failure undergoing continuous ambulatory peritoneal dialysis (CAPD) following administration of 500 mg of each drug intraperitoneally with the dialysis solution. Data from one patient was unsatisfactory due to initial problems with the assay procedure. Data from the remaining three patients showed that both drugs were rapidly absorbed from the peritoneal cavity and achieved similar peak concentrations in the serum. Clearance of the drug was facilitated by changing the dialysate for drug-free dialysis solution at 8 and 12 hours after the initial administration. Although ampicillin was cleared slightly more rapidly than sulbactam, the relative concentrations of the drugs remained within the optimum range for antibacterial synergy in both dialysate and serum for the 24 hour period monitored. Antibacterially effective concentrations were still present at the end of this 24 hour period.

Study #95-1
Title: The Distribution of Sulbactam and Ampicillin into Subcutaneous Tissue Fluid in Human Volunteers

Investigators: B. Hoffstedt, M.D., S. Haidl, M.D. and M. Walder, M.D., Department of Clinical Bacteriology and Infectious Diseases, General Hospital, Malmo, Sweden.

Procedure: Mean concentrations of sulbactam and ampicillin in subcutaneous tissue fluid, following a single intravenous dose of sulbactam (0.5 g) plus ampicillin (1.0 g) were determined in eight healthy volunteers. Blister fluid was obtained from two volunteers only, and this fluid was assayed only for sulbactam.

Penetration of both sulbactam and ampicillin into subcutaneous tissue fluid was rapid and elimination (t 1/2 about 0.9 hr for both drugs) was very similar to the rate of elimination from the blood. The peak concentrations in this fluid were 4.2 mg/liter for sulbactam and 8.1 mg/liter for ampicillin. The peak concentration of sulbactam in blister fluid was 13.9 mg/liter, with a half-life of 1.1 hours. Brown et al detected even higher concentrations of sulbactam in cantharides-induced blister fluid. This type of blister is probably associated with a greater inflammatory reaction.

Studies #11-1 and 12-1
Title: Penetration of Sulbactam into Cerebrospinal Fluid

Investigators: George A. Pankey, M.D., Ochsner Clinic, New Orleans, LA and Charles V. Sanders, M.D., Louisiana State University

Procedure: Ten patients undergoing diagnostic lumbar puncture were given 1.0 g sulbactam and 2.0 g cefoperazone by one hour IV infusions. Following completion of the dose, a sample of CSF and a sample of serum were drawn at approximately the same time. These samples were analyzed for sulbactam and cefoperazone by bioassay.

Results
The serum concentrations of sulbactam between 3 and 30 minutes after the end of the infusion ranged from 11.1 to 19.3 mcg/ml. CSF concentrations were very low, between undetectable (below 0.02 mcg/ml) and 0.075 mcg/ml. Cefoperazone concentrations in serum were 48.5 to 87.2 mcg/ml and less than 1.0 mcg/ml in CSF.

In two patients with bacterial meningitis, the CSF concentrations of sulbactam were 7% and 9% of the serum concentration; one with viral meningitis had a CSF concentration 7% that of the serum. Another subject with post-trauma meningitis had relatively higher concentrations of sulbactam in CSF: two CSF samples had sulbactam concentrations 14% and 32% of the serum concentrations.

These studies demonstrate that in subjects with normal meninges sulbactam penetration into the CSF appears to be low. However, in subjects with inflamed meninges, sulbactam penetration into CSF is increased.

Study 36-1: The Elimination of Sulbactam Alone and Sulbactam Plus Ampicillin in Subjects with Renal Dysfunction

Investigators: Dr. N. Wright, FRCP and Dr. R. Wise, MD MRCPath, Dudley Road Hospital, Birmingham, UK

Sulbactam (500 mg) was given as a single intravenous bolus injection to 11 subjects with various degrees of renal dysfunction (GFR range, 3-93 ml/min). The serum half-life of sulbactam ranged from 1.1 hours in those with near normal renal function to 21.3 hours in those with terminal renal failure.
The same dose of sulbactam was co-administered with 500 mg ampicillin to 5 subjects with various degrees of renal dysfunction (GFR range, 4-48 ml/min). The serum half-life of sulbactam increased from 1.5 hours in the subject with least renal impairment to 14 hours in the most renally-impaired subject. The corresponding serum half-lives of ampicillin were 1.8 and 19 hours.
The elimination constant of sulbactam increased linearly with creatinine clearance and was not affected by the presence of ampicillin.
The volume of distribution of sulbactam showed no significant change between the various groups of patients with differing renal function and approximated to an overall value of 9.0 liters.

Based on these results, the investigators recommend that in subjects with renal failure the dose of sulbactam/ampicillin should be reduced to twice daily in patients with GFRs between 15 and 30 ml/min, once daily for GFRs between 5 and 14 ml/min, and every second day for those with GFRs of less than 5 ml/min.

Study #82-1
Title: An Open Pharmacokinetic Study to Determine the Ratio of Sulbactam and Ampicillin in Bile Following Intravenous Administration of a Fixed Ration (1:2) Combination of the Drugs

Investigators: Dr. R.J. Walker, FRCP and Dr. M.P. Ghimire, Walton Hospital, Rice Lane, Liverpool

Procedure: Six adult subjects requiring duodenal intubation for pancreatic function testing were entered in this study.
Each subject received sulbactam (250 mg) plus ampicillin (500 mg) intravenously by bolus injection approximately two hours before duodenal intubation. Duodenal aspirates containing firstly gall bladder bile, and then predominantly hepatic bile, were collected from all subjects. Blood samples were also taken during the same period for the determination of drug concentration in serum.

Results: Sulbactam and ampicillin concentrations were satisfactorily determined in aspirates from 5 of the 6 subjects.
Concentrations of sulbactam in bile were usually lower than serum concentrations, indicating the absence of active secretion.
The ratio of sulbactam to ampicillin concentrations in bile was lower than the ratio present in the administered dose and consistently less than the ratio present in serum.
Sulbactam, therefore, appeared to be less readily transported into the bile than ampicillin.

Study #69-1
Title: A Pharmacokinetic Study to Determine the Transplacental Transfer and the Effect of Labor on Maternal Serum Concentrations of Sulbactam and Ampicillin Administered as a Single IV Dose

Investigator: Professor R. Lambotte, Clinique Gynecologique et Obstetricale, Hospital de Baviere, Liege, Beligum

Procedure: Sixty-nine women in advanced pregnancy participated in this study. Sulbactam and ampicillin were co-administered in a single intravenous dose to each subject at times ranging from 3 minutes to about 6 hours before delivery. The doses given were 1.0 g sulbactam plus 1.0 g ampicillin to the first 10 subjects and 0.5 g sulbactam plus 1.0 g ampicillin to the remaining 59 subjects. Blood samples were taken from each subject at various intervals after dosing until delivery, when a final sample was taken together with a sample of the cord blood. A sample of the infant's urine was collected, whenever possible, immediately after birth, and amniotic fluid was obtained from one patient. Assays for sulbactam only were carried out on the samples from the first 53 patients. Assays for both sulbactam and ampicillin were carried out on the samples from the last 16 subjects.

Results: Mean serum concentrations of sulbactam were 63.8 mg/L and 45.7 mg/L following the 1.0 g and the 0.5 g doses, respectively, at the earliest time (0.17 - 0.25 hrs) after administration. The corresponding ampicillin concentration was 59.9 mg/L after a 1.0 g dose.
The calculated serum half-lives (0.60-0.65 hours for sulbactam, 0.48 hours for ampicillin) were significantly less than those usually recorded in normal subjects (aproximatley 1 hour for both drugs).
There was rapid transplacental transfer of both sulbactam and ampicillin with antibacterially-effective concentrations being detected in cord blood serum within 0.2 hours of dosing. Concentrations of both drugs in cord blood were similar to the concentrations in venous blood from about one hour and thereafter following dosing. The high concentrations of sulbactam and ampicillin detected in cord blood serum indicated that both drugs readily traverse the placental barrier. Sulbactam was detected in all samples of infant urine, and ampicillin was present in the two samples on which ampicillin assays were carried out.
The one ammiotic fluid sample contained 48.7 mg/L of sulbactam and 43.1 mg/L of ampicillin.

Study 14-1: The Kinetics of Ampicillin/Sulbactam in Puerperal Women

Investigator: Lauri D. Thrupp, M.D., University of California, Irvine, Orange, CA

Procedure: Eleven women who had failed to respond to doses of 2 g cephalothin every 4 hours or 2 g ampicillin every six hours were included in this study. These patients, most of whom had undergone cesarean section delivery, were continued on cephalothin or ampicillin and also were given 500 mg or 1 g sulbactam, administered by 20 minute infusions every 6 hours. Following one of the doses, serum, urine, and/or milk samples were obtained and assayed for sulbactam and ampicillin.

Results: The mean of the highest concentrations of sulbactam following the infusion of 500 mg was about 19 mcg/ml. Following the infusion of 1.0 g, the mean of the highest concentrations was approximately 44 mcg/ml. Half-lives of approximately 1 hour were observed for both sulbactam and ampicillin.
The mean concentration in milk samples taken between 0 and 8 hours post dose was 0.52 mcg/ml for sulbactam and 1.67 mcg/ml for ampicillin.

Fitting of the sulbactam data to a pharmacokinetic two-compartment open model gave a mean value for the apparent volume of distribution of the central compartment of approximately 180 ml/kg and the apparent whole body volume of distribution was approximately 450 ml/kg. Approximately 40% of the drug was in the central compartment in the post-distributive phase.

The plasma clearance of sulbactam was 290 ml/min; the renal clearance was 220 ml/min. The steady-state volume of distribution (Vd_{ss}) was approximately 18.1 liters (268 ml/kg).

The ampicillin data could not be fitted to a two-compartment model. The whole body volume of distribution was estimated by extrapolation of the elimination phase data to time equals 0. Following the correction for the infusion time, the apparent volume of distribution was large (51.1 liters, or 900 ml/kg). The steady-state volume of distribution was 27 liters (476 ml/kg), and the total body clearance of the drug was 457 ml/min. This was substantially greater than that of sulbactam.
The steady-state volume of distribution of sulbactam was similar to that of normal males, suggesting that equal dose regimens will produce serum concentrations in puerperal women similar to those of male volunteers.

Study 24-1: Penetration of Ampicillin and Sulbactam into Prostate Tissue

Investigator: Paul Madsen, M.D., Urology Section, V.A. Hospital, Madison, Wisconsin

Procedure: Twenty-six patients about to undergo prostatectomy were given 1.0 g ampicillin plus 0.5 g sulbactam by IM injection for prophylaxis against infection. During the surgery, samples of serum, urine and prostate tissue were obtained and assayed for sulbactam and ampicillin.

Results:
The serum concentrations of sulbactam and ampicillin were similar with mean concentrations of approximately 7 mcg/ml sulbactam and 8 mcg/ml ampicillin.
The mean prostate concentration of sulbactam was 19.8 mcg/g (range = 5.2-46.2 mcg/g).
The mean ampicillin concentration was 2.35 mcg/g (range = 0.4 - 9.3 mcg/g).

Study 21-1: Penetration of Sulbactam and Ampicillin into Appendix Tissue

Investigator: Thomas V. Berne, M.D., LAC/USC Medical Center, Los Angeles, CA

Procedure: Prior to an emergency appendectomy, two patients received an IV dose of 2.0 g ampicillin plus 1.0 g sulbactam by intravenous infusion for prophylaxis against infection. The appendix was divided into several samples by the Pathology Department of the University of Southern California. Additionally, a simultaneous sample of peritoneal fluid was obtained from one patient. The samples were assayed for ampicillin and sulbactam.

Results:
The mean tissue concentrations were 40 mcg/g sulbactam and 3.2 mcg/g ampicillin in one of the patients. In the other patient, mean tissue concentrations were 29 mcg/g sulbactam and 0.8 mcg/g ampicillin. Appreciable concentrations of sulbactam and ampicillin were found in peritoneal fluid.

Study 89-1: An Open non-comparative Study of Efficacy, Saftey and Pharmacokinetics of Sulbactam Plus Ampicillin in Urinary Tract Infections in Children

Investigator: Dr. O. Johansson, Malmo Allmanna Hospital, Malmo, Sweden

Procedure: Four children (1 male, 3 female) aged 11-18 months, with a clinical diagnosis of acute pyelonephritis were treated with sulbactam at approximately 100 mg/kg/day (300-350 mg doses) in combination with ampicillin in a 1:2 ratio, in divided doses by IV bolus injection 8-hourly for 2-3 days. Two children continued treatment with sultamicillin suspension 200 mg 8-hourly for 2 and 3 days, respectively.

Pharmacokinetic Results: Mean maximum serum concentrations of 85 mg/L and 178 mg/L were recorded for sulbactam and ampicillin, respectively. The elimination half-lives of sulbactam (0.92 hours) and ampicillin (0.83 hours) were essentially the same as those obtained previously in health adult volunteers at the same hospital. Mean AUCs were proportional to the dose administered (86.6 mg/L.h for sulbactam and 180.5 mg/L.hr for ampicillin), emphasizing further the similarity of the pharmacokinetic properties of both drugs.

The similar clearance rate of both drugs (61.4 ml/mir for sulbactam and 57.9 ml/min for ampicillin) was consistent with predominantly renal clearance, as has been demonstrated in adults.

Efficacy Results
Two children had insignificant growth of mixed organisms in their urine samples and were deemed unevaluable.
Both assessable patients were clinically and bacteriologically (*E. coli*) cured.

Side Effects
One child developed skin rashes 2 hours after injections 2, 3 and 4, and therapy was discontinued.

Study 88-1: A Pharmacokinetic Study of Sulbactam Plus Ampicillin in Bile from the Common Bile Duct

Investigator: D. L. Morris, M.D., FRCS, Department of Surgery, University Hospital, Nottingham

Procedure: Six hospitalized patients with T-tube drainage of the common bile duct each received a single dose of sulbactam (0.5 g) plus ampicillin (1.0 g) by intravenous bolus injection. Bile, via the T-tube, was collected during various time intervals after dosing and blood samples were taken at the mid-point of each bile collection.

Results: Pharmacokinetic data for one subject were inadequate and not included in the analysis. Maximum biliary concentration of sulbactam ranged from 4.4 - 41.2 mg/L (mean 19.4 mg/L) and of ampicillin from 105.6 - 1412.6 mg/L) (mean 470.8 mg/L), occurring at 0.5 -1.0 hours after dosing. Biliary excretion was a minor route of elimination for both drugs accounting for about 0.24% (range 0.05 -0.61%) of the administered dose of sulbactam and 2.81% (range 0.47-8.04) of that of ampicillin. Antibacterially-effective concentrations of both drugs were attained in the bile from all five subjects.

Study 77-1: An Open Non-Comparative Study to Assess the Pharmacokinetics, Efficacy and Safety of a Combination of Sulbactam with Ampicillin in the Treatment of Acute Exacerbations of Chronic Bronchitis

Investigators: Dr. F. Maesen and Dr. B. Davies, De Wever Ziekenhuis, Heerlen, The Netherlands.

Procedure: Twenty patients (14 male, 6 female) with acute purulent exacerbations of chronic bronchitis were treated in this open non-comparative study wi. ampicillin plus sulbactam. The dose was 1.0 g ampicillin plus 0.5 g sulbactam, dissolved with 2% lignocaine and given bid by IM injection. The mean duration of treatment was 9.9 days. In 10 patients, for the purpose of pharmacokinetic studies, the first day's doses were doubled, patients receiving two injections, one in each buttock.

Pharmackinetic Results:
Mean peak serum concentrations of sulbactam (13.3 mg/L) and ampicillin (16.5 mg/L) occurred about 1 hour after dosing in the low dose group of patients. The corresponding peak concentrations of 23.5 mg/L and 20.6 mg/L were achieved at a similar time after dosing in the high dose group of patients.
Peak sputum concentrations of both drugs were detected 2-3 hours later and were about one-tenth of the peak serum concentrations.
A comparison of the AUCs (0-7 hr) for sputum and serum indicated that sulbactam and ampicillin penetrate into the sputum to a similar extent (13.7% and 12.4% for sulbactam, 13.0% and 9.3% for ampicillin, in the low dose and high dose groups of patients, respectively).

Efficacy Results:
At the end of treatment, 16/18 patients showed a satisfactory clinical and bacteriological response. At follow-up the proportion was 12/18.

Side Effects:
No local or systemic side effects were reported in this study.

Clinical Studies

I. Controlled Studies (Domestic)

1- Study #18-1
Title: A Single Blind Comparative Study of Sulbactam/Ampicillin and Clindamycin/Tobramycin Combinations in Surgical Infections

Investigator: Frank E. Jones, M.D., Medical College of Wisconsin

Study Design:
This was a third party blinded comparative trial of the safety and efficacy of a 1:2 ratio of sulbactam and ampicillin and tobramycin/clindamycin regimens in surgical patients with serious intra-abdominal infections.

Patients
A total of 5 patients were enrolled in this study. Three were randomized to the sulbactam/ampicillin group and two to the clindamycin/tobramycin treatment group.

Dermographic Summary

Age (years)	Sulbactam/Ampicillin	Clindamycin/Tobramycin
Range	27-55	24-72
Mean	39.6	48.0
Sex		
Male	0	2
Female	3	0

Dose and Route of Administration
Sulbactam 1.0 g and ampicillin 2.0 g were coadministered by intravenous infusion every six hours.
Clindamycin 600 mg was administered by intravenous infusion every six hours and tobramycin, 1.5 mg/kg, by intravenous infusion every eight hours.

To blind the 8 hourly tobramycin administration, and equal volume of physiological saline was administered every 8 hours to patients assigned to the sulbactam/ampicillin combination.

Duration of Therapy

	Sulbactam/Ampicillin	Clindamycin	Tobramycin
1 dose	2 patients	-	-
4 doses	-	1 patient	1 patient
6 days	-	1 patient	1 patient
12 days	1 patient	-	-

EVALUATION

EFFICACY

No. of Cases Evaluable	0
No. of Cases Unevaluable	5

Reasons Cases Unevaluable
Sulbactam/Ampicillin Group
Inadequate duration of treatment - 2 patients
No susceptibility testing done - 1 patient

Clindamycin/Tobramycin Group
Inadequate duration of treatment - 2 patients
One of these patients had a negative pre-treatment culture; the other patient died 24 hours after having received only 4 doses of tobramycin and six of clindamycin.

SAFETY
There were no side effects which in the investigator's opinion were related to sulbactam/ampicillin or clindamycin/tobramycin therapy.

There were no abnormal laboratory test values reported in either treatment group.

Conclusions
It is impossible to reach at any conclusions from this study, since there were no evaluable cases in the sulbactam/ampicillin group.

2- Study #23-1
Title: A Blind Comparative Trial of Parenteral Sulbactam Sodium Coadministered with Ampicillin Versus Clindamycin/Gentamicin Coadministered in the Treatment of Endomyometritis Encountered After Cesarean Section

Investigators: R. David Miller, M.D. and Louri D. Thrupp, M.D., University of California, Irvine

Study Design:
This was a third party blinded comparative trial of the efficacy and safety of a 1:2 ratio of sulbactam and ampicillin and a clindamycin/gentamicin regimen in the treatment of endomyometritis following cesarean section, other infections following gynecological surgical procedures and pelvic inflammatory disease.

Patients
A total of 48 patients were enrolled in this study; 21 were assigned by random selection to the sulbactam/ampicillin group and 27 to the clindamycin/gentamicin group.

Demographic Summary

	Sulbactam/Ampicillin	Clindamycin/Gentamicin
Age (years)		
Range	18-38	14-67
Mean	27.1	29.7
Sex		
Male	0	0
Female	21	27

Dose and Route of Administration

Sulbactam 1.0 g and ampicillin 2.0 g were coadministered by intravenous infusion every six hours. Clindamycin 600 mg was administered by intravenous infusion every six hours and gentamicin, 1.2 mg/kg, by intravenous infusion every eight hours.

To blind the eight hourly gentamicin administration, an equal volume of physiological saline was administered every 8 hours to patients assigned to the sulbactam/ampicillin combination.

Duration of Therapy

Days	Sulbactam/Ampicillin	Clindamycin/Gentamicin
1	0	1
2 - 3	12	14
4 - 5	8	7
6 - 7	1	4
10	0	1

EVALUATION

EFFICACY

	Sulbactam/Ampicillin	Clindamycin/Gentamicin
No. of Cases Evaluable	9	13
No. of Cases Unevaluable	12	14

Reasons Cases Unevaluable

Sulbactam/Ampicillin Group

No pre-treatment pathogen	- 6 patients
No pre-treatment culture	- 1 patient
No susceptibility testing done	- 1 patient
Inadequate duration of therapy	- 3 patients
No follow-up culture	- 1 patient

Clindamycin/Gentamicin Group

No pre-treatment pathogen	- 5 patients
No susceptibility testing done	- 2 patients
Inadequate cultures	- 3 patients
Concomitant effective antibiotic	- 2 patients
Treatment discontinued because of age	- 1 patient
No gynecologic infection	- 1 patient

RESULTS

INFECTION	SULBACTAM/AMPICILLIN				CLINDAMYCIN/GENTAMICIN			
		CLINICAL RESPONSE				CLINICAL RESPONSE		
GYNECOLOGIC	No.	CURE	IMP	FAIL	No.	CURE	IMP	FAIL
Endometritis	9	7(78%)	1(11%)	1(11%)	10	7(70%)	1(10%)	2(20%)
Vaginal cuff inf	-				3	3(100%)		

AMPICILLIN-SENSITIVE ORGANISMS	SULBACTAM/AMPICILLIN No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERAD	CLINDAMYCIN/GENTAMICIN No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERAD
G. vaginalis	8	8 (100%)		6	6 (100%)	
Peptococcus spp.	1	1 (100%)		2	2 (100%)	
Peptostreptococcus spp.	1	1 (100%)		-		
S. aureus	-			1	1 (100%)	
Enterococci	-			7	6 (86%)	1 (14%)
E. coli	-			2	1 (50%)	1 (50%)
Enterobacter spp.	-			1	1 (100%)	
Bacteroides spp.	-			2	2 (100%)	
AMPICILLIN-RESISTANT ORGANISMS						
E. coli	-			1	1 (100%)	
P. aeruginosa	-			1	0	1 (100%)

SAFETY

SULBACTAM/AMPICILLIN GROUP

No. of Patients - 21
No. of Patients with Local Side Effects: - 1 (5%)
No. of Patients with Systemic Side Effects - 3 (14%)

SYSTEMIC SIDE EFFECTS

Chest pain - 1 (5%)
Flatulence - 1 (5%)
Diarrhea - 2 (10%)

LOCAL SIDE EFFECTS

Pain at IV injection site - 1 (5%)

CLINDAMYCIN/GENTAMICIN GROUP

No. of Patients - 27
No. of Patients with Local Side Effects - 0
No. of Patients with Systemic Side Effects - 3 (11%)

SIDE EFFECTS

Dizziness - 1 (3.7%)
Tachycardia - 1 (3.7%)
Breathlessness - 1 (3.7%)
Diarrhea - 1 (3.7%)
Nausea - 1 (3.7%)
Vomiting - 1 (3.7%)
Headache - 2 (7%)

Abnormal Laboratory Tests

Sulbactam/Ampicillin Group

Increased eosinophils - 2
Increased SGOT - 1
Increased SGPT - 4

Conclusions: Results of this study show that sulbactam/ampicillin was clinically effective in 8/9 (88.9%) patients with endometritis.

Clindamycin/gentamicin treatment was clinically effective in 8/10 (80%) patients with endometritis.

Sulbactam/ampicillin eradicated 10/10 (100%) ampicillin-sensitive organisms, and clindamycin/gentamicin eradicated 19/21 (90.5%) ampicillin-sensitive organisms.

However, there were no ampicillin-resistant organisms isolated in the patients treated with sulbactam/ampicillin; therefore, it is not possible to assess the comparative efficacy of the two treatment regimens in this type of infections.

3- Study #21-1

Title: A Double-blind Comparative Study of Parenteral Sulbactam Sodium/Ampicillin versus Clindamycin/Gentamicin Coadministered in Cases of Peritonitis Associated with Appendicitis

Investigators: Thomas V. Berne, M.D. and Albert E. Yellin, M.D., LAC/USC Medical Center, Los Angeles, California

Study Design:
This was a third party blind (by hospital pharmacy) comparative study to assess the efficacy and safety of parenteral sulbactam sodium coadministered with ampicillin sodium in the treatment of peritonitis associated with gangrenous or perforated appendicitis and to compare it with clindamycin/gentamicin therapy
Antimicrobial therapy was started prior to laparotomy, but only patients found to have peritonitis were continued on the assigned drug regimen.

Patients
A total of 196 patients were enrolled in this study; 131 were assigned by random selection to the sulbactam/ampicillin treatment group and 65 to the clindamycin/gentamicin group.

Demographic Summary

	Sulbactam/Ampicillin	Clindamycin/Gentamicin
Age (years)		
Range	17-63	18-45
Mean	27.38	26.12
Sex		
Male	99	48
Female	32	17

Dose and Route of Administration
Sulbactam 1.0 g and ampicillin 2.0 g were coadministered by intravenous infusion every six hours.
Clindamycin 600 mg was administered by intravenous infusion every six hours and gentamicin, 1.5 mg/kg, by intravenous infusion every 8 hours.

To blind the eight hourly gentamicin administration, an equal volume of physiological saline was administered every 8 hours to patients assigned to the sulbactam/ampicillin combination.

Duration of Therapy

Days	Sulbactam/Ampicillin	Clindamycin/Gentamicin
1	42	23
2 - 3	21	5
4 - 5	27	17
6 - 7	33	16
8 -10	5	2
11 -14	3	2

EVALUATION

EFFICACY

	Sulbactam/Ampicillin	Clindamycin/Gentamicin
No. of Cases Evaluable	58	33
No. of Cases Unevaluble	73	32

Reasons Cases Unevaluable
Sulbactam/Ampicillin Group

No culture taken - 3 patients
No pre-treatment pathogen - 6 patients
Resistant organism isolated - 4 patients
No peritonitis found - 56 patients
Patients found to be allergic to penicillin - 1 patient
Concomitant antibiotic given - 1 patient
Treatment discontinued at patient's request - 1 patient
Wrong drugs given by nurse and treatment discontinued - 1 patient

Clindamycin/Gentamicin Group

No pre-treatment pathogen - 6 patients
No peritonitis found - 26 patients

RESULTS

INFECTION	SULBACTAM/AMPICILLIN CLINICAL RESPONSE				CLINDAMYCIN/GENTAMICIN CLINICAL RESPONSE			
INTRA-ABDOMINAL	No.	CURE	IMP	FAIL	No.	CURE	IMP	FAIL
	58	52(90%)	2(3%)	4(7%)	33	33(100%)		

AMPICILLIN-SENSITIVE ORGANISMS	SULBACTAM/AMPICILLIN BACTERIOLOGIC RESPONSE No.	ERADICATED	NOT ERAD	CLINDAMYCIN/GENTAMICIN BACTERIOLOGIC RESPONSE No.	ERADICATED	NOT ERAD
Streptococcus spp.	1	1 (100%)		-		
S. viridans	5	5 (100%)		4	4 (100%)	
Group D streptococci	1	1 (100%)		-		
E. coli	32	30 (94%)	2 (6%)	17	17 (100%)	
C. freundii	1	1 (100%)		-		
Lactobacillus spp.	2	2 (100%)		2	2 (100%)	
C. perfringens	1	1 (100%)		2	2 (100%)	
P. magnus	3	3 (100%)		-		
Eubacterium spp.	1	1 (100%)		1	1 (100%)	
Propionibacterium spp.	1	1 (100%)		-		
Fusobacterium spp.	1	1 (100%)		1	1 (100%)	
F. nucleatum	1	1 (100%)		1	1 (100%)	
Bacteroides spp.	5	5 (100%)		-		
B. fragilis	6	6 (100%)		6	6 (100%)	
B. distasonis	4	4 (100%)		2	2 (100%)	
B. vulgatus	-			1	1 (100%)	
Citrobacter spp.	-			1	1 (100%)	
Alcaligenes spp.	-			1	1 (100%)	
K. oxytoca	-			1	1 (100%)	
K. pneumoniae	-			1	1 (100%)	

AMPICILLIN-RESISTANT ORGANISMS	BACTERIOLOGIC RESPONSE No.	ERADICATED	NOT ERAD	BACTERIOLOGIC RESPONSE No.	ERADICATED	NOT ERAD
Alcaligenes spp.	-			1	1 (100%)	
E. coli	18	18 (100%)		9	9 (100%)	
E. aerogenes	1	1 (100%)		-		
E. cloacae	3	3 (100%)				
H. alvei	-			1	1 (100%)	
K. pneumoniae	3	3 (100%)		3	3 (100%)	
K. oxytoca	3	3 (100%)		1	1 (100%)	
A. faecalis	1	1 (100%)				
Aeromonas spp.	1	1 (100%)				
P. aeruginosa	12	12 (100%)		3	3 (100%)	
Citrobacter spp.	1	1 (100%)				
C. freundii	2	2 (100%)		1	1 (100%)	
Bacteroides spp.	10	10 (100%)				
B. fragilis	17	16 (94%)	1 (6%)	6	6 (100%)	
B. distasonis	11	11 (100%)		10	10 (100%)	
B. vulgatus	-			1	1 (100%)	
B. thetaiotaomicron	-			4	4 (100%)	

In the sulbactam/ampicillin group, 2 patients developed superinfections, and 2 developed reinfections.

SAFETY

SULBACTAM/AMPICILLIN GROUP
No. of Patients: 131
No. with Local Side Effects - 7 (5.3%)
No. with Systemic Side Effects - 10 (7.6%)

SIDE EFFECTS

LOCAL

Pain at IV injection site	1 (0.8%)
Phlebitis	7 (5.3%)

SYSTEMIC

Chest pain/tightness/pressure	1 (0.8%)
Diarrhea	9 (6.8%)
Vomiting	1 (0.8%)
Retention of urine	1 (0.8%)
Rash	1 (0.8%)
Epistaxis	1 (0.8%)
Edema	1 (0.8%)

CLINDAMYCIN/GENTAMICIN GROUP

No. of Patients - 65
No. with Local Side Effects - 3 '4.6%)
No. with Systemic Side Effects - 3 (4.6%)

SIDE EFFECTS

LOCAL

Phlebitis	3 (4.6%)

SYSTEMIC

Diarrhea	2 (3.0%)
Rash	1 (1.5%)

Abnormal Laboratory Tests

Sulbactam/Ampicillin Group

Decreased Hgb	17
Decreased Hct	13
Decreased RBCs	8
Decreased neutrophils	1
Increased eosinophils	12
Increased bosophils	3
Increased lymphocytes	2
Decreased lymphocytes	7
Increased monocytes	10
Increased bilirubin	1
Increased SGOT	30
Increased SGPT	33
Increased LDH	22
Increased alk. phosphatase	9
RBCs in urine	4
Hyaline casts in urine	1

Clindamycin/Gentamicin Group

Decreased Hgb	8
Decreased Hct	7
Decreased RBCs	3
Increased WBCs	3
Increased eosinophils	6
Increased bosophils	3
Decreased lymphocytes	5
Increased monocytes	2
Increased SGOT	15
Increased SGPT	12
Increased LDH	14
Increased alk. phosphatase	7
Increased creatinine	1
Increased urine pH	2
Albumin in urine	1
RBCs in urine	1
Hyaline casts in urine	2
Granular casts in urine	2

Conclusions:
Results of this study demonstrate that sulbactam/ampicillin was clinically effective in 54/58 (93%) patients with peritonitis.
Clindamycin/gentamicin treatment was clinically effective in 33/33 (100%) patients with peritonitis.

Sulbactam/ampicillin eradicated 63/65 (96.9%) ampicillin-sensitive organisms and 82/83 (98.8%) ampicillin-resistant organisms.
Clindamycin/gentamicin eradicated 41/41 (100%) ampicillin-sensitive organisms and 40/40 (100%) ampicillin-resistant organisms.

Local side effects were similar in both treatment groups.
Systemic side effects were somewhat higher in the sulbactam /ampicillin group, mainly due to a 6.8% incidence of diarrhea.

This study demonstrates that sulbactam/ampicillin is as safe and effective as clindamycin/gentamicin in the treatment of patients with acute peritonitis.

4- Study #98-1
Title: A Single-blind Comparative Study of Parenteral Sulbactam/Ampicillin versus Clindamycin/Gentamicin Coadministered in Pediatric Cases of Intra-Abdominal Anaerobic and Polymicrobic Infections.

Investigator: Stephen C. Aronoff, M.D., Rainbow Babies and Children's Hospital

Study Design:
This is a third party blinded comparative study designed to determine the efficacy and safety of intravenous sulbactam/ampicillin combination therapy in pediatric cases with appendicitis and peritonitis and to compare it with a clindamycin/gentamicin regimen.

Patients:
Only 10 patients completed this study which is continuing; 5 were randomized to the sulbactam/ampicillin group and 5 to the clindamycin/gentamicin group.

Demographic Summary

	Sulbactam/Ampicillin			Clindamycin/Gentamicin	
	Years	No. Patients		Years	No. Patients
Age Range	2-5	3	Age Range	4-6	3
	16	2		13-17	2
Mean Range	8.6		Mean Age	8.8	

Sex	Sulbactam/Ampicillin	Clindamycin/Gentamicin
Male	3	4
Female	2	1

Dose and Route of Administration

Sulbactam 50 mg/kg/day and ampicillin 200 mg/kg/day were coadministered by intravenous infusion in equally divided doses every 6 hours. Gentamicin 2.5 mg/kg every 8 hours was also administered until the susceptibility of baseline isolates to the sulbactam/ampicillin mixture was established. Clindamycin 40 mg/kg/day in equally divided doses every 6 hours and gentamicin 2.5 mg/kg every 8 hours were administered to patients randomly assigned to the comparative group.

To blind the eight hourly gentamicin administration, an equal volume of physiological saline was administered every 8 hours to patients assigned to the sulbactam/ampicillin combination.

Duration of Therapy

Sulbactam/Ampicillin		Clindamycin/Gentamicin	
Days	No. Pts	Days	No. Pts
4-6	2	2	1
7	1	7	2
15-17	2	8-10	2

EVALUATION

EFFICACY	Sulbactam/Ampicillin	Clindamycin/Gentamicin
No. of Cases Evaluable	0	4
No. of Cases Unevaluable	5	1

Reasons Cases Unevaluable
Sulbactam/Ampicillin Group
No pre-treatment pathogen - 2 cases
Concomitant gentamicin therapy - 3 cases

Clindamycin/Gentamicin Group
No pre-treatment pathogen - 1 case

RESULTS
Since none of the patients in the sulbactam/ampicillin group were evaluable, this study is not valid for evaluation of comparative drug efficacy.

SAFETY

Sulbactan/Ampicillin Group
No. of Patients: 5
No. of Patients with Local Side Effects: 0
No. of Patients with Systemic Side Effects: 0

Clindamycin/Gentamicin Group
No. of Patients: 5
No. of Patients with Local Side Effects: 0
No. of Patients with Systemic Side Effects: 1

SIDE EFFECT
Diarrhea - 1 patient

Abnormal Laboratory Tests
Sulbactam/Ampicillin Group
Increased eosinophils - 1

Clindamycin/Gentamicin Group
Increased SGOT - 1
Increased SGPT - 1

Conclusions: This study is not valid for the evaluation of comparative efficacy, since there were no evaluable cases in the sulbactam/ampicillin group.

There were no local side effects in either group, and only one patient in the sulbactam/ampicillin group developed diarrhea.

5- Study #25-1
Title: A Comparative Study of Parenteral Sulbactam/Ampicillin Versus Ampicillin and Chloramphenicol in the Treatment of Meningitis in Infants and Children

Investigator: W.J. Rodriguez, M.D., Children's Hospital National Medical Center, Washington, D.C.

Coinvestigators: J.R. Pu[illegible], M.D. and J. Feris, M.D., Santo Domingo, Dominican Republic

Study Design:
This is an ongoing study designed as an open, randomized comparative trial of the safety and efficacy of sulbactam/ampicillin and a conventional chloramphenicol/ampicillin regimen in the treatment of meningitis in infants and children.

Following performance of baseline physical and laboratory tests and having obtained an informed consent, patients were randomly assigned to receive either sulbactam/ampicillin or ampicillin and chloramphenicol.
A lumbar tap was done on all patients prior to the administration of the test drugs, and samples were subjected to established methods of examination utilizing both direct and cultural techniques.
Isolates were tested for antimicrobic susceptibility by in vitro disc (Kirby-Bauer) and minimal inhibitory concentration (MIC) tests.
Beta-lactamase production was determined on H. influenzae isolates and on other isolates as appropriate.

Patients:
Thirty-six patients were entered into this study; 18 were assigned to the sulbactam/ampicillin group and 18 to the chloramphenicol/ampicillin group.

Demographic Summary

Age	Sulbactam/Ampicillin	Chloramphenicol/Ampicillin
1- 2 ms	2 patients	2 patients
3-11 ms	8 patients	11 patients
1-2 yrs	4 patients	3 patients
3-4 yrs	3 patients	1 patient
9 yrs	1 patient	1 patient
Sex		
Male	11 patients	8 patients
Female	7 patients	10 patients

Dose and Route of Administration
Sulbactam/ampicillin was administered by intravenous infusion at a dosage of 400 mg/kg/day of ampicillin and 50 mg/kg/day of sulbactam, in equally divided doses every 4 hours. Ampicillin was administered by intravenous infusion at a dosage of 400 mg/kg/day, in equally divided doses every 4-6 hours.
Chloramphenicol was administered by I.V. bolus, over 3-5 minutes, at a dosage of 100 mg/kg/day in four equally divided doses.
In patients who were proven not to have H. influenzae meningitis, chloramphenicol was discontinued and either ampicillin therapy maintained or Penicillin G started.

Duration of Therapy

Days	Sulbactam/Ampicillin	Ampicillin	Chloro	Pen G
1	0	1	2	0
2- 4	5	5	9	0
5- 7	2	1	4	0
8-10	[illegible]	3	1	0
11-13	6	6	2	1
14-16	0	0	0	0
17-18	1	2	0	0

EVALUATION

EFFICACY

	Sulbactam/Ampicillin	Chloro/Ampicillin
No. of Cases Evaluable	11	10
No. of Cases Unevaluable	7	8
Reason Cases Unevaluable		
No pre-treatment pathogen	7	5
Concomitant antibiotic		1
Inadequate duration of therapy (death)		2

RESULTS

INFECTION	No.	Sulbactam/Ampicillin CLINICAL RESPONSE CURE	Sulbactam/Ampicillin CLINICAL RESPONSE FAIL	Chloro/Ampicillin Clinical Response No.	Chloro/Ampicillin Clinical Response CURE
Meningitis	11	10(91%)	1*(9%)	10	10(100%)

AMPICILLIN-SENSITIVE ORGANISMS	No.	BACT. RESPONSE ERADICATED	No.	BACT. RESPONSE ERADICATED
H. influenzae	6	6 (100%)	6	6 (100%)
S. pneumoniae	2	2 (100%)	3	3 (100%)
Neisseria spp.	1	1 (100%)	-	-
AMPICILLIN-RESISTANT ORGANISMS				
H. influenzae	2	2 (100%)	1	1 (100%)

*The one case considered as a clinical failure was a two-year old retarded hydrocephalic child with an Arnold-Chiari malformation. A ventriculo-peritoneal shunt was in place since birth. On the fourth day of therapy, the attending physician reviewed the results of the culture collected following 48 hours of sulbactam/ampicillin treatment and decided to change the patient to chloramphenicol regimen since the CSF still grew out an ampicillin resistant H. influenzae. However, the CSF culture collected on the last day of sulbactam/ampicillin was subsequently reported as sterile.

SAFETY

Sulbactam/Ampicillin Group
No. of Patients - 18
No. of with Local Side Effects - 1 (5.5%)
No. with Systemic Side Effects - 1 (5.5%)

SIDE EFFECTS
LOCAL
Pain at IV injection site - 1 (55%)

SYSTEMIC
Bleeding from oral and rectal
Mucosas and venipuncture site - 1 (5.5%)

Chloramphenicol/Ampicillin Group
No side effects were reported

N 50608 -2

Deaths

There were two deaths reported in the chloramphenicol/ampicillin group. One patient died on the third day of treatment and the other after having received only 3 doses.

Abnormal Laboratory Tests

Sulbactam/Ampicillin Group

Increased eosinophils	- 3
Increased SGOT	- 1
Increased SGPT	- 1
Increased alk. phosphatase	- 1
Increased prothrombin time	- 1

Chloramphenicol/Ampicillin Group

Increased eosinophils	- 1

Special Parameters

Simultaneous samples of serum and CSF, obtained predose and at the end of the intravenous infusion, were taken when possible and assayed for sulbactam and, when sample size was adequate, for ampicillin content. In patients where no baseline pathogens were isolated (4), the ratios of CSF/serum concentrations were low (6%). In patient where baseline bacterial pathogens were isolated (12), the ratios of CSF/serum concentrations were higher (avg. 26%)

Conclusions:

Sulbactam/ampicillin was clinically effective in 10/11 (91%) children with meningitis.
Chloramphenicol/ampicillin was clinically effective in 10/10 (100%) children with meningitis.

Sulbactam/ampicillin eradicated 9/9 (100%) ampicillin-sensitive organisms and 2/2 (100%) ampicillin-resistant organisms.
Chloramphenicol/ampicillin eradicated 9/9 (100%) ampicillin sensitive organisms and 1/1 (100%) ampicillin-resistant organisms.

This study is considered inadequate to support the efficacy of sulbactam/ampicillin in the treatment of meningitis in children due to ampicillin-resistant H. influenzae (only 2 cases).

6- Protocol "A"

Title: A Third Party Blinded Multicenter Comparative Study of parenteral Sulbactam/Ampicillin versus Clindamycin and an Aminoglycoside Coadministered in Cases of Anaerobic and Polymicrobic Infections.

Investigators:

1 - Ian Baird, M.D., Riverside Methodist Hospital, Columbus, OH

2 - Nicolas V. Christou, M.D., Ph.D., Royal Victoria Hospital, Montreal Canada

3 - Charles Ericsson, M.D., University of Texas Health Sciences Center, Houston, TX

4 - Sydney M. Finegold, M.D., Wadsworth Hosptial Center, Los Angeles, CA

5 - John Gunning, M.D., Harbor/UCLA Medical Center, Torrance, CA

6 - W. Dean Hidy, M.D., St. Francis Hospital, Tulsa, OK

7 - Brent Stromberg, M.D., Medical University of South Carolina, Charleston, SC

Study Design:
This study was designed as a third party blinded (by hospital pharmacy), randomized, comparative trial of the safety and efficacy of sulbactam/ampicillin and clindamycin and aminoglycoside regimen in patients with a diagnosis of an anaerobic or polymicrobic infection.

Patients:
A total of 133 patients were entered into this ongoing study. Sixty-seven were randomized to receive sulbactam/ampicillin and 66 to receive clindamycin/aminoglycoside. The number of patients contributed by each investigator was as follows:

Investigator		Sulbactam/Ampicillin	Clindamycin/Aminoglycoside
Baird		7	6 (clindamycin/gentamicin)
Ericsson		1	2 (clindamycin/gentamicin)
Gunning		23	24 (clindamycin/gentamicin)
Hidy		1	1 (clindamycin/gentamicin)
Finegold		2	1 (clindamycin/gentamicin)
Christou		1	2 (clindamycin/netilmycin)
Stromberg		32	29 (clindamycin/tobramycin)
	Total	67	65*

* One patient received clindamycin alone

Demographic Summary

Age (years)	Sulbactam/Ampicillin	Clindamycin/Aminoglycoside
Range	17-99	16-89
Mean	39.4	40.9
Sex		
Male	24	25
Female	43	41

Dose and Route of Administration
Sixty-seven patients were assigned by random selection to receive therapy with 1 g sulbactam and 2 g of ampicillin administered as an intravenous infusion every six hours.
Sixty-six patients were assigned to receive 600 mg clindamycin every 6 hours by intravenous infusion together with 1.5 mg/kg gentamicin (34 patients), 1.5 mg/kg tobramycin (29 patients) or 1.8 mg/kg netilmycin (2 patients) by intravenous infusion every eight hours.
One patient received clindamycin alone.

To blind the eight hourly aminoglycoside administration, an equal volume of physiological saline was administered every eight hours to patients assigned to the sulbactam/ampicillin combination.

Duration of Therapy Days	Sulbactam/Ampicillin	Clindamycin/Aminoglycoside
1	1	2
2 - 3	14	17
4 - 5	21	12
6 - 7	13	13
8 -10	8	9
11 -14	5	10
15 -21	4	1
30	-	1
55	1	-
Total	67	65*

*One patient received clindamycin alone for 16 days.

EVALUATION

EFFICACY

	Sulbactam/Ampicillin	Clindamycin/Aminoglycoside
No. of Cases Evaluable	34	36
No. of Cases Unevaluable	33	30

Reasons Cases Unevaluable

	Sulbactam/Ampicillin	Clindamycin/Aminoglycoside
No pre-treatment pathogen	6	10
Resistant baseline pathogen	1	4
No pre-treatment culture	1	-
No in-vitro susceptibility done	9	2
Less than 48 hours of therapy	3	3
Concomitant antibiotic	2	2
No follow-up culture	10	6
Received only clindamycin	-	1
Treatment discontinued due to side effects	-	-
	1	2

RESULTS

	SULBACTAM/AMPICILLIN				CLINDAMYCIN/AMINOGLYCOSIDE			
	CLINICAL RESPONSE				CLINICAL RESPONSE			
INFECTION	No.	CURE	IMP	FAIL	No.	CURE	IMP	FAIL
INTRA-ABDOMINAL								
Abscess	2	2(100%)			1		1(100%)	
SKIN & SKIN STRUCTURE								
Ulcer	6	1	4	1	13	7	4	2
Cellulitis	2	1	1				2	
Wound infection	3	1	2		2	2		
Gangrene	1	1			1		1	
Infected cyst	1	1			-			
Abscess	8	7	1		4		3	1
Infected burn	-				2	1		1
Total	21	12(57.1%)	8(38.1%)	1(4.8%)	24	10(41.7%)	10(41.7%)	4(16.6%)
INFECTION GYNECOLOGIC								
Salpingitis	9	8		1	8	7		1
Parametritis					1	1		
Total	9	8(88.9%)		1(11.1%)	9	8(88.9%)		1(11.1%)
LOWER RESPIRATORY								
Lung Abscess	1	1			1	1		
Pneumonia	1		1		1			1
Total	2	1 (50%)	1(50%)		2	1(50%)		1(50%)

INTRA-ABDOMINAL AMPICILLIN-SENSITIVE ORGANISMS	SULBACTAM/AMPICILLIN BACTERIOLOGIC RESPONSE No.	ERADICATED	NOT ERAD	CLINDAMYCIN/AMINOGLYCOSIDE BACTERIOLOGIC RESPONSE No.	ERADICATED	NOT ERAD
S. viridans	1	1 (100%)		-		
Enterococcus	-			1		1 (100%)
E. coli	1	1 (100%)		-		
B. fragilis	1	1 (100%)		-		
AMPICILLIN-RESISTANT ORGANISMS						
S. epidermidis	1	1 (100%)		-		
P. rettgeri	-			1	1 (100%)	
M. morganii	-			1		1 (100%)
E. cloacae	-			1	1 (100%)	
C. freundii	-			1	1 (100%)	
K. pneumoniae	-			1	1 (100%)	

SKIN & SKIN STRUCTURE AMPICILLIN-SENSITIVE ORGANISMS	SULBACTAM/AMPICILLIN BACTERIOLOGIC RESPONSE No.	ERADICATED	NOT ERAD	CLINDAMYCIN/AMINOGLYCOSIDE BACTERIOLOGIC RESPONSE No.	ERADICATED	NOT ERAD
Coag-negative staph	2	2 (100%)		-		
S. epidermidis	1		1 (100%)			
S. aureus	3	3 (100%)		1	1 (100%)	
S. viridans	-			1	1 (100%)	
Group B strep	1	1 (100%)		-		
Enterococci	3	3 (100%)		7	5 (71.4%)	2 (28.6%)
Corynebacterium	1		1 (100%)	2	2 (100%)	
E. coli	4	4 (100%)		6	4 (66.7%)	2 (33.3%)
P. mirabilis	7	6 (85.7%)	1 (14.3%)	9	4 (44.4%)	5 (55.6%)
P. rettgeri	-			1	1 (100%)	
E. cloacae	1	1 (100%)		-		
E. agglomerans	-			1	1 (100%)	
K. pneumoniae	1	1 (100%)		-		
A. lwoffi	-			1	1 (100%)	
Propionibacterium sp.	1	1 (100%)		-		
Peptostreptococcus sp.	2	2 (100%)		1	1 (100%)	
Bacteroides sp.	1	1 (100%)		3	3 (100%)	
B. fragilis	1	1 (100%)		1	1 (100%)	

(table continued)

SKIN & SKIN STRUCTURE	SULBACTAM/AMPICILLIN			CLINDAMYCIN/AMINOGLYCOSIDE		
AMPICILLIN-RESISTANT	BACTERIOLOGIC RESPONSE			BACTERIOLOGIC RESPONSE		
ORGANISMS	No.	ERADICATED	NOT ERAD	No.	ERADICATED	NOT ERAD
Coag-negative staph	2	1 (50%)	1 (50%)	1	1 (100%)	
S. aureus	6	4 (66.7%)	2 (33.3%)	9	6 (66.7%)	3 (33.3%)
E. coli	3	3 (100%)		1		1 (100%)
P. mirabilis	1	1 (100%)		-		
P. vulgaris	-			1		1 (100%)
P. stuartii	-			1	1 (100%)	
Providencia sp.	1		1 (100%)	1	1 (100%)	
M. Morganii	2	2 (100%)		2	1 (50%)	1 (50%)
K. pneumoniae	2	1 (50%)		2	2 (100%)	
E. cloacae	-			2	2 (100%)	
A. anitratus	2	2 (100%)		-		
Achromobacter sp.	1	1 (100%)		-		
Corynebacterium sp.	-			1	1 (100%)	
C. diversus	-			1	1 (100%)	
C. freundii	-			1	1 (100%)	
S. marcescens	1	1 (100%)		2	2 (100%)	
Aeromonas sp.	-			1		1 (100%)
P. aeruginosa	4	1 (25%)	3 (75%)	5	3 (60%)	2 (40%)
C. perfringens	1	1 (100%)		-		
B. fragilis	4	4 (100%)		2	1 (50%)	1 (50%)

GYNECOLOGIC INFECTIONS AMPICILLIN-SENSITIVE	BACTERIOLOGIC RESPONSE			BACTERIOLOGIC RESPONSE		
ORGANISMS	No.	ERADICATED	NOT ERAD	No.	ERADICATED	NOT ERAD
S. viridans	1	1 (100%)		-		
S. pyogenes	1	1 (100%)		-		
Group B strep.	1	1 (100%)		-		
Diphtheroids	1	1 (100%)		-		
E. coli	1	1 (100%)		1	1 (100%)	
Pseudomonas sp.	-			1	1 (100%)	
N. gonorrhoeae	4	4 (100%)		7	7 (100%)	
Peptococcus sp.	-			1	1 (100%)	
Peptostreptoccus sp.	2	2 (100%)		2	2 (100%)	
AMPICILLIN-RESISTANT ORGANISMS						
S. epidermidis	1	1 (100%)		-		
S. viridans	1	1 (100%)		-		
Gamma strep.	1	1 (100%)		-		
E. coli	1	1 (100%)		-		
K. oxytoca	1	1 (100%)		-		
N. gonorrhoeae	1	1 (100%)		-		
B. fragilis	5	5 (100%)		-		

LOWER RESPIRATORY	SULBACTAM/AMPICILLIN			CLINDAMYCIN/AMINOGLYCOSIDE		
AMPICILLIN-SENSITIVE	BACTERIOLOGIC RESPONSE			BACTERIOLOGIC RESPONSE		
ORGANISMS	No.	ERADICATED	NOT ERAD	No.	ERADICATED	NOT ERAD
E. coli	1	1 (100%)		-		
P. mirabilis	1		1 (100%)	-		
Peptostreptococcus sp.	1	1 (100%)		2	2 (100%)	

Table continued

LOWER RESPIRATORY AMPICILLIN-SENSITIVE ORGANISMS	SULBACTAM/AMPICILLIN No.	SULBACTAM/AMPICILLIN BACTERIOLOGIC RESPONSE ERADICATED	SULBACTAM/AMPICILLIN BACTERIOLOGIC RESPONSE NOT ERAD	CLINDAMYCIN/AMINOGLYCOSIDE No.	CLINDAMYCIN/AMINOGLYCOSIDE BACTERIOLOGIC RESPONSE ERADICATED	CLINDAMYCIN/AMINOGLYCOSIDE BACTERIOLOGIC RESPONSE NOT ERAD
Eubacterium sp.	-			2	2 (100%)	
Peptostreptococcus sp.	-			1	1 (100%)	
F. nucleatum	1	1 (100%)		-	-	
Bacteroides sp.	2	2 (100%)		1	1	
AMPICILLIN-RESISTANT ORGANISMS						
E. coli	1	1 (100%)		-		
M. morganii	1		1 (100%)	-		
K. pneumoniae	-			1	1 (100%)	
A. anitratus	1	1 (100%)		-		

SAFETY
Sulbactam/Ampicillin Group
No. of Patients - 67
No. with Local Side Effects - 0
No. with Systemic Side Effects - 7 (10.4%)

SYSTEMIC SIDE EFFECTS
Nausea - 1 (1.5%)
Diarrhea - 3 (4.5%)
Itching - 2 (2.9%)
Rash - 2 (2.9%)
Yeast infection - 1 (1.5%)

Clindamycin/Aminoglycoside Group
No. of Patients - 66
No. with Local Side Effects - 0
No. with Systemic Side Effects - 4 (6.1%)

Systemic Side Effects
Fever - 1 (1.5%)
Rash - 1 (1.5%)
Itching - 1 (1.5%)
Chest pain, shortness of breath, tachycardia - 1 (1.5%)
Yeast infections - 1 (1.5%)

Deaths
One patient in the clindamycin/aminoglycoside group died after 5 days of therapy. The investigator considered this death not drug related.

Abnormal Laboratory Tests

	Sulbactam/Ampicillin	Clindamycin/Aminoglycoside
Decreased Hgh	4	4
Decreased Hct	3	4
Decreased RBcs	2	2
Increased eosinaphils	6	6
Increased platelets	1	1
Decreased platelets	1	1

table continued

	SULBACTAM/AMPICILLIN	CLINDAMYCIN/AMINOGLYCOSIDE
Increased SGOT	7	9
Increased SGPT	7	6
Increased alk. phosphatase	3	3
Increased bilirubin	-	1
Increased BUN	-	4
Increased creatinine	-	2

Conclusions

Sulbactam/ampicillin was clinically effective in 2/2 (100%) patients with intra-abdominal abscesses, in 20/21 (95%) patients with skin and skin structure infections, in 8/9 (89%) patients with gynecologic infections and in 2/2 (100%) with lower respiratory infections.
Clindamycin plus an aminoglycoside was clinically effective in 1/1 (100%) patient with an intra-abdominal abscess, 20/24 (83%) with skin and skin structure infections, 8/9 (89%) with gynecologic infections and 2/2 (100%) with lower respiratory infections.

In intra-abdominal infections, sulbactam/ampicillin eradicated 3/3 (100%) ampicillin - sensitive organisms and 1/1 (100%) ampicillin-resistant organism; in skin and skin structure infections eradicated 26/29 (90%) ampicillin-sensitive organisms and 22/30 (73%) ampicillin-resistant organisms; in gynecologic infections eradicated 11/11 (100%) ampicillin-sensitive organisms and 11/11 (100%) ampicillin-resistant organisms and in lower respiratory infections eradicated 5/6 (83%) ampicillin-sensitive organisms and 2/3 (67%) ampicillin-resistant organisms.

In intra-abdominal infections, clindamycin plus an aminoglycoside eradicated 0/1 ampicillin-sensitive organism and 4/5 (80%) ampicillin-resistant organisms; in skin and skin structure infections eradicated 25/34 (74%) ampicillin-sensitive organisms and 23/33 (70%) ampicillin-resistant organisms; in gynecologic infections eradicated 11/11 (100%) ampicillin-sensitive organisms (there were no patients with ampicillin-resistant organisms), and in lower respiratory infections eradicated 6/6 (100%) ampicillin-sensitive organisms and 1/1 (100%) ampicillin-resistant organism.

There were no local side effects in either group. The incidence of systemic side effects was somewhat higher in the sulbactam-ampicillin group, again due to a higher incidence of diarrhea.

Results of this study demonstrate that sulbactam/ampicillin is as safe and effective as clindamycin plus an aminoglycoside in the treatment of patients with skin and skin structure and gynecologic infections.
A comparison of the efficacy in patients with intra-abdominal and lower respiratory infections is not possible, due to the small number of patients in each treatment group.

7- Protocol "B"
Title: A Third Party Blinded Multicenter Comparative Study of Parenteral Sulbactam/Ampicillin versus Metronidazole/Aminoglycoside Coadministered in Cases of Anaerobic and Polymicrobic Infections

Investigators

1 - Nicolas V. Christou, M.D., Ph.D., Royal Victoria Hospital, Montreal, Canada

2 - Charles B. Hanna, M.D., Spartanburg General Hospital, Spartanburg, SC

3 - George A. Pankey, M.D., Alton Ochsner Medical Foundation, New Orleans, LA

4 - R. Orahood, M.D., Grady Memorial Hospital, Delaware, OH

5 - Richard L. Sweet, M.D., San Francisco General Hospital, San Francisco, CA

Study Design

This study was designed as a third party blinded (by hospital pharmacy), randomized, comparative trial of the safety and efficacy of a 1:2 ratio of sulbactam and ampicillin and a metronidazole/aminoglycoside regimen in patients with a diagnosis of an anaerobic or polymicrobic infection.

Patients

A total of 34 patients were entered into this ongoing study. Sixteen were randomized to the sulbactam/ampicillin group and 18 to the metronidazole/aminoglycoside group.

The number of patients contributed by each investigator was as follows:

Investigator	Sulbactam/Ampicillin	Metronidazole/Gentamicin
Christou	1	0
Hanna	10	12
Orahood	1	1
Pankey	1	0
Sweet	3	5

Demographic Summary

Age (years)	Sulbactam/Ampicillin	Metronidazole/Gentamicin
Range	13-79	16-87
Mean	39.6	45.3
Sex		
Male	8	8
Female	8	10

Dose and Route of Administration

Sixteen patients were assigned by random selection to receive therapy with 1 g sulbactam and 2 g ampicillin administered as an intravenous infusion every six hours.

Eighteen patients were assigned to receive a 15 mg/kg loading dose of metronidazole and 7.5 mg/kg thereafter every 6 hours by intravenous infusion together with 1.5 mg/kg gentamicin by intravenous infusion every eight hours.

To blind the eight hourly gentamicin administration an equal volume of physiological saline was administered every eight hours to patients assigned to the sulbactam/ampicillin combination.

Duration of Therapy

Days	Sulbactam/Ampicillin	Metronidazole/Aminoglycoside
1	1	1
2 - 3	4	3
4 - 5	3	6
6 - 7	3	7
8 -10	3	1
13	1	-
26	1	-

EVALUATION

EFFICACY

	Sulbactam/Ampicillin	Metronidazole/Gentamicin
No. of Cases Evaluable	3	6
No. of Cases Unevaluable	13	12

Reasons Cases Unevaluable

	Sulbactam/Ampicillin	Metronidazole/Gentamicin
No. pre-treatment pathogen	4	2
No pre-treatment culture	1	2
Resistant baseline pathogen	3	1
No in-vitro susceptibility done	3	-
Treatment less than 48 hours	1	-
No follow-up culture	1	7

RESULTS

	SULBACTAM/AMPICILLIN				METRONIDAZOLE/GENTAMICIN			
		CLINICAL RESPONSE				CLINICAL RESPONSE		
INFECTION	No.	CURE	IMP	FAIL	No.	CURE	IMP	FAIL
INTRA-ABDOMINAL								
Abscess	1			1	-			
Peritonitis	-				1	1		
Total	1			1 (100%)	1	1 (100%)		
SKIN & SKIN STRUCTURE								
Ulcer	2	1	1		1		1	
Abscess	-				3	2	1	
Cellulitis	-				1		1	
Total	2	1 (50%)	1 (50%)		5	2 (40%)	3 (60%)	

INTRA-ABDOMINAL AMPICILLIN-SENSITIVE ORGANISMS	SULBACTAM/AMPICILLIN	BACTERIOLOGIC RESPONSE		METRONIDAZOLE/GENTAMICIN	BACTERIOLOGIC RESPONSE	
	No.	ERADICATED	NOT ERAD	No.	ERADICATED	NOT ERAD
Klebsiella sp.	1		1 (100%)	-		
B. fragilis	-			1	1 (100%)	
SKIN & SKIN STRUCTURE AMPICILLIN-SENSITIVE ORGANISMS						
S. aureus	-			1		1 (100%)
E. coli	1	1 (100%)		1	1 (100%)	
P. mirabilis	-			1		1 (100%)
S. faecalis	-			1		1 (100%)
AMPICILLIN-RESISTANT ORGANISMS						
S. aureus	-			2	1 (50%)	1 (50%)
E. cloacae	1	1 (100%)		-		
A. anitratus	1	1 (100%)		-		
B. fragilis	-			1	1 (100%)	

SAFETY
No local or systemic adverse reactions were reported in either treatment group.

Deaths
One patient in the sulbactam/ampicillin group died on the 4th day of therapy. The investigator considered this death not drug related.

Abnormal Laboratory Tests

	Sulbactam/Ampicillin	Metronidazole/Gentamicin
Decreased Hgb	2	-
Decreased Hct	1	1
Decreased RBCs	-	1
Increased eosinophils	-	2
Decreased lymphocytes	-	1
Increased SGOT	3	-
Increased SGPT	1	-

Conclusions:
Sulbactam/ampicillin was clinically ineffective in 1/1 (100%) patient with an intra-abdominal abscess and effective in 2/2 (100%) patients with skin and skin structure infections.
Metronidazole/gentamicin was clinically effective in 1/1 (100%) patient with peritonitis and in 5/5 (100%) patients with skin and skin structure infections.

In one patient with an intra-abdominal abscess, sulbactam/ampicillin did not eradicate one ampicillin-sensitive organism isolated and in skin and skin structure infections eradicated 1/1 (100%) ampicillin-sensitive organism and 2/2 (100%) ampicillin-resistant organisms.

In one patient with peritonitis, metronidazole/gentamicin eradicated 1/1 (100%) ampicillin-sensitive organism and in skin and skin structure infections eradicated 1/4 (25%) ampicillin-sensitive organism and 2/3 (67%) ampicillin-resistant organism.

No local or systemic side effects were reported in either treatment group.

This comparative study is considered inadequate due to the small number of evaluable cases included in each treatment group.

8- Protocol #93-1
Title: A Partially Blinded Comparative Study of Parenteral Sulbactam/Ampicillin versus Cefoxitin Coadministered in Cases of Anaerobic and Polymicrobic Infections.

Investigator: William Holloway, M.D., Wilmington Medical Center, Wilmington, DE

Study Design
This study was designed as a third party blinded (by hospital pharmacy), randomized, comparative trial of the safety and efficacy of sulbactam and ampicillin in a 1:2 ratio and a cefoxitin regimen in patients with a diagnosis of anaerobic/polymicrobic infections.

Patients
A total of 31 patients were entered into this ongoing study. Sixteen patients were randomized to be treated with sulbactam/ampicillin and 15 to be treated with cefoxitin.

Demographic Summary

Age (years)	Sulbactam/Ampicillin	Cefoxitin
Range	17-63	15-62
Mean	29.8	31.8
Sex		
Male	6	5
Female	10	10

Dose and Route of Administration
Sixteen patients were assigned by random selection to receive therapy with 1 g of sulbactam and 2 g of ampicillin administered as an intravenous infusion every six hours.
Fifteen patients were assigned to receive 2 g of cefoxitin every four hours by intravenous infusion.

Duration of Therapy

Days	Sulbactam/Ampicillin	Cefoxitin
2 - 3	1	-
4 - 5	5	6
6 - 7	8	7
9	2	1
11	-	1

EVALUATION

EFFICACY

	Sulbactam/Ampicillin	Cefoxitin
No. of Cases Evaluable	12	9
No. of Cases Unevaluable	4	6

Reasons Cases Unevaluable

	Sulbactam/Ampicillin	Cefoxitin
No pre-treatment pathogen	1	[illegible]
No post-treatment culture	2	2
Treatment less than 48 hours (Attending physician wanted to treat the patient with a more conventional therapy)	1	
No susceptibility testing done	-	2

RESULTS

	SULBACTAM/AMPICILLIN				CEFOXITIN			
		CLINICAL RESPONSE				CLINICAL RESPONSE		
INFECTION	No.	CURE	IMP	FAIL	No.	CURE	IMP	FAIL
GYNECOLOGIC								
PID	2	2			1	1		
Endometritis	5	5			3	3		
Total	7	7 (100%)			4	4 (100%)		
INTRA-ABDOMINAL								
Peritonitis					1	1 (100%)		
Rectal abscess	1	1 (100%)						
SKIN & SKIN STRUCTURE								
Cellulitis	1	1						
Wound infection	1		1					
Ulcer	1		1					
Abscess	1		1		4	2	2	
Total	4	1 (25%)	3(75%)		4	2 (50%)	2 (50%)	

GYNECOLOGIC AMPICILLIN-SENSITIVE ORGANISMS	SULBACTAM/AMPICILLIN No.	SULBACTAM/AMPICILLIN BACTERIOLOGIC RESPONSE ERADICATED	SULBACTAM/AMPICILLIN BACTERIOLOGIC RESPONSE NOT ERAD	CEFOXITIN No.	CEFOXITIN BACTERIOLOGIC RESPONSE ERADICATED	CEFOXITIN BACTERIOLOGIC RESPONSE NOT ERAD
Streptococcus sp.	1	1 (100%)		–		
Group B streptococcus	5	5 (100%)		2	2 (100%)	
Enterococcus	1	1 (100%)		1	1 (100%)	
E. coli	1	1 (100%)		–		
Bacteroides sp	–			1	1 (100%)	
AMPICILLIN-RESISTANT						
S. epidermidis				1	1 (100%)	
E. coli	1	1 (100%)		1	1 (100%)	
INTRA-ABDOMINAL AMPICILLIN-SENSITIVE						
Enterococcus	1	1 (100%)		–		
P. mirabilis	1	1 (100%)		–		
E. coli	–			1	1 (100%)	
AMPICILLIN -RESISTANT						
E. coli	1	1 (100%)		–		
B. fragilis	1	1 (100%)		–		
SKIN & SKIN STRUCTURE AMPICILLIN-SENSITIVE ORGANISMS						
Coagulase-negative Staph	1	1 (100%)		–		
S. aureus	1	1 (100%)		–		
Streptococcus sp.	–			2	2 (100%)	
S. viridans	–			1	1 (100%)	
Group B streptococcus	1	1 (100%)		–		
Enterococcus	1	1 (100%)		2	2 (100%)	
B. melaninogenicus	–			1	1 (100%)	
AMPICILLIN-RESISTANT						
S. aureus	1		1 (100%)	1	1 (100%)	
S. epidermidis	1	1 (100%)		1	1 (100%)	
E. coli	–			1	1 (100%)	
E. cloacae	1	1 (100%)		–		
Acinetobacter sp.	1	1 (100%)		–		
A. anitratus	1	1 (100%)		–		
Flavobacterium sp.	1	1 (100%)		–		
B. fragilis	1	1 (100%)		1	1 (100%)	

SAFETY

Sulbactam/Ampicillin Group
No side effects were reported

Cefoxitin Group
No side effects were reported

Abnormal Laboratory Tests	Sulbactam/Ampicillin	Cefoxitin
Increased eosinophils	2	1
Increased platelets	1	-
Increased CPK	-	2

Conclusions:
Sulbactam/ampicillin treatment was clinically effective in 7/7 (100%) gynecologic infections, in 1/1 (100%) intra-abdominal infection and in 4/4 (100%) skin and skin structure infections.
Cefoxitin treatment was clinically effective in 4/4 (100%) gynecologic infections, 1/1 (100%) intra-abdominal infections and in 4/4 (100%) skin and skin structure infections.

In gynecologic infections, sulbactam/ampicillin eradicated 8/8 (100%) ampicillin-sensitive organisms and 1/1 (100%) ampicillin-resistant organisms; in intra-abdominal infections eradicated 2/2 (100%) ampicillin-sensitive organisms and 2/2 (100%) ampicillin-resistant organisms and in skin and skin structure infections eradicated 4/4 (100%) ampicillin-sensitive organisms and 6/7 (85.7%) ampicillin-resistant organisms.
In gynecologic infections, cefoxitin eradicated 4/4 (100%) ampicillin-sensitive organisms and 2/2 (100%) ampicillin-resistant organisms; in intra-abdominal infections eradicated 1/1 (100%) ampicillin-sensitive organism and in skin and skin structure infections eradicated 6/6 (100%) ampicillin-sensitive organisms and 4/4 (100%) ampicillin-resistant organisms.

No side effects were reported in either treatment group.

Although the number of patients in each disease category is too small to allow for a comparative evaluation, it is apparent that both treatment regimens were safe and effective in the conditions treated.

9- Protocol #15-1
Title: A Third Party Blinded Comparative Study of Parenteral Sulbactam/Ampicillin versus Moxalactam Administered in Cases of Biliary Tract Sepsis.

Investigators: Albert E. Yellin, M.D. and John M. Leedom, M.D., LAC-USC Medical Center, Los Angeles, CA

Study Design
This study was designed as a third party blinded (by hospital pharmacy), randomized, comparative trial of the efficacy and safety of parenteral sulbactam and ampicillin in the treatment of patients with bilary tract sepsis and to compare it with a standard moxalactam therapeutic regimen.

Patients
A total of 31 patients were entered into this ongoing study. Fifteen patients were randomized to the sulbactam/ampicillin treatment and 16 to the moxalactam treatment.

Demographic Summary

Age (years)	Sulbactam/Ampicillin	Moxalactam
Range	21-62	23-65
Mean	40.3	37

Sex		
Male	3	4
Female	12	12

Dose and Route of Administration
Fifteen patients were assigned by random selection to receive therapy with 1 g of sulbactam and 2 g of ampicillin administered by intravenous infusion every six hours.
Sixteen patients were assigned to receive 2 g of moxalactam every six hours by intravenous infusion.

Duration of Therapy

Days	Sulbactam/Ampicillin	Moxalactam
1	1	2
2 - 3	1	5
4 - 5	3	3
6 - 7	4	3
8 -10	4	3
11 -14	2	-

EVALUATION

EFFICACY

	Sulbactam/Ampicillin	Moxalactam
No. of Cases Evaluable	3	3
No. of Cases Unevaluable	12	13

Reasons Cases Unevaluable

	Sulbactam/Ampicillin	Moxalactam
No pre-treatment pathogen	10	8
No pre-treatment culture	-	2
No susceptibility testing done	1	-
No biliary tract infection	1	3

RESULTS

INFECTION	Sulbactam/Ampicillin Clinical Respone No.	Sulbactam/Ampicillin Clinical Respone Cure	Moxalactam Clinical Response No.	Moxalactam Clinical Response Cure
INTRA-ABDOMINAL				
Cholecystitis	3	3 (100%)	3	3 (100%)

ORGANISMS	Bacteriologic Response No.	Bacteriologic Response ERAD	Bacteriologic Response No.	Bacteriologic Response ERAD
AMPICILLIN-SENSITIVE				
Lactobacillus sp	1	1 (100%)	1	1 (100%)
E. coli	1	1 (100%)	1	1 (100%)
S. faecalis	2	2 (100%)		
C. freundii	1	1 (100%)	1	1 (100%)
AMPICILLIN-RESISTANT				
S. epidermidis	1	1 (100%)	-	
S. aureus	-		1	1 (100%)

SAFETY

Sulbactam/Ampicillin Group
No. of Patients - 15
No. with Local Side Effects - 1 (6.7%)
No. with Systemic Side Effects - 1 (6.7%)

Local Side Effect
Itching - 1 (6.7%)

Moxalactam Group
No. of Patients - 16
No. with Local Side Effects - 1 (6.3%)
No. with Systemic Side Effects - 3 (18.8%)

Local Side Effect
Phlebitis - 1 (6.3%,

Systemic Side Effects
Confusion - 1 (6.3%)
Diarrhea - 1 (6.3%
Vomiting - 1 (6.3%)
Itching - 1 (6.3%)
Rash - 1 (6.3%)
Hiccoughs - 1 (6.3%)

Abnormal Laboratory Tests
No drug related abnormal values were reported in either treatment group.

Conclusions:
Sulbactam/ampicillin treatment was clinically effective in 3/3 (100%) intra-abdominal infections. Moxalactam treatment was clinically effective in 3/3 (100%) intra-abdominal infections.

Sulbactam/ampicillin eradicated 5/5 (100%) ampicillin-sensitive organisms and 1/1 (100%) ampicillin-resistant organism.

Moxalactam eradicated 3/3 (100%) ampicillin-sensitive organisms and 1/1 (100%) ampicillin-resistant organism.

Local side effects were similar in both treatment groups. A higher incidence of systemic side effects was reported in the moxalactam treated group.

This comparative study is considered inadequate due to the small number of evaluable cases included in each treatment group.

II. Uncontrolled Studies (7 Domestic, 1 Canadian)

1- Study #02-1
Title: An Open Study of Parenteral Sulbactam/Ampicillin

Investigator: Joseph F. Plouffe, M.D., Ohio State University

Study Design
Open, noncomparative study to determine the efficacy and safety of sulbactam sodium combined with ampicillin in the treatment of patients with respiratory, urinary and skin and skin structure infections.

Patients
Thirty patients were entered in this study

Demographic Summary of All Patients

Age (years)
Range - 18-79
Mean - 39.07

Sex
Male - 17 patients
Female - 13 patients

Dose and Route of Administration
Sulbactam sodium and ampicillin were administered by intravenous infusion every six hours in the following ratios of sulbactam to ampicillin:
500: 500 - 18 patients
500: 1000 - 7 patients
500: 1500 - 1 patients
500: 2000 - 4 patients

Duration of Therapy

Days	No. of Patients
2 - 3	3
4 - 5	11
6 - 7	10
8 -10	4
11 -14	2

EVALUATION

EFFICACY
No. of Cases Evaluable - 20
No. of Cases Unevaluable - 10

Reasons Cases Unevaluable

No pre-treatment pathogen	- 2
Colony count less than 10^5	- 1
Resistant organism isolated	- 1
No pre-treatment culture	- 2
No post-treatment culture	- 3
Concomitant antibiotic	- 1

RESULTS

INFECTION SKIN & SKIN STRUCTURE	No.	CLINICAL RESPONSE CURE	IMPROVE
Cellulitis	12	10	2
Abscess	3	2	1
Ulcer	1		1
Total	16	12 (75%)	4 (25%)

LOWER RESPIRATORY			
Bronchitis	1	1	
Pneumonia	2	1	1
Total	3	2 (67%)	1 (33%)

INFECTION URINARY TRACT	No.	CLINICAL RESPONSE CURE	IMPROVE
(Uncomplicated)	1	-	1 (100%)

SKIN AND SKIN STRUCTURE AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
S. pyogenes	5	5 (100%)
Streptococcus spp.	1	1 (100%)
S. aureus	1	1 (100%)
S. epidermidis	1	1 (100%)
P. mirabilis	1	1 (100%)
E. cloacae	1	1 (100%)
Peptococcus spp.	2	2 (100%)
AMPICILLIN-RESISTANT ORGANISMS		
S. aureus	8	8 (100%)
S. epidermidis	1	1 (100%)
Staphylococcus spp.	1	1 (100%)
K. pneumoniae	1	1 (100%)

LOWER RESPIRATORY AMPICILLIN-SENSITIVE ORGANISM	No.	BACTERIOLOGIC RESPONSE ERADICATED
H. influenzae	1	1 (100%)

LOWER RESPIRATORY AMPICILLIN-SENSITIVE ORGANISM	No.	BACTERIOLOGIC RESPONSE ERADICATED
H. influenzae	1	1 (100%)
AMPICILLIN-RESISTANT ORGANISM		
H. influenzae	2	2 (100%)
URINARY TRACT (uncomp) AMPICILLIN-SENSITIVE		
E. coli	1	1 (100%)

The patient with urinary tract infection developed a P. mirabilis superinfection.

SAFETY
No. of patients evaluable - 30
No. of patients with local side effects - 0
No. of patients with systemic side effects - 2 (6.7%)

SIDE EFFECTS
Abdominal distention - 1 (3%)
Rash - 1 (3%)

Abnormal Laboratory Tests

Decreased Hct	- 1
Decreased RBC	- 1
Increased eosinophils	- 5
Increased basophils	- 1
Increased SGOT	- 1
Increased GGT	- 1
Hyaline casts in urine	- 1

2- Study #04-1
Title: An Open Study of Parenteral Sulbactam Sodium/Ampicillin

Investigator: Joseph J. Timmes, M.D., Director of Surgery, Jersey City Medical Center

Study Design:
Open noncomparative study to determine the efficacy and safety of a combination of parenteral sulbactam sodium and ampicillin in the treatment of various skin and soft tissue infections.

Patients
Fifteen patients were entered in this study.

Demographic Summary of All Patients

Age (years)

Range	- 18-77
Mean	- 42.6

Sex	
Male	- 11 patients
Female	- 4 patients

Dose and Route of Administration

All patients were administered 500 mg sulbactam sodium and 500 mg ampicillin sodium every six hours by intravenous infusion (10 patients) or intramuscular injection (5 patients).

Duration of Therapy

Days	No. of Patients
4 - 5	4
6 - 7	4
8 -10	4
13 -14	2
18	1

EVALUATION

EFFICACY

No. of Cases Evaluable - 13
No. of Cases Unevaluable - 2

Reasons Cases Unevaluable

No pre-treatment pathogen - 1
No pre-treatment culture - 1

RESULT

INFECTION SKIN & SKIN STRUCTURE	No.	CLINICAL RESPONSE CURE	IMPROVE
Cellulitis	5	5	-
Abscess	6	5	1
Wound infection	1	1	-
Infected ulcer	1	-	1
Total	13	11 (85%)	2 (15%)

SKIN & SKIN STRUCTURE AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
S. viridans	1	1 (100%)	-
S. pyogenes	2	2 (100%)	-
Staphylococcus spp.	1	1 (100%)	-
E. coli	1	1 (100%)	-
P. mirabilis	1	1 (100%)	-
E. cloacae	1	1 (100%)	-
Salmonella type B	1	1 (100%)	-
AMPICILLIN-RESISTANT ORGANISMS			
S. aureus	4	4 (100%)	
E. coli	1	-	1 (100%)
P. mirabilis	1	1 (100%)	
Enterobacter spp.	1	1 (100%)	

SAFETY

No. of patients evaluable - 15
No. of patients with local side efffects - 0
No. of patients with systemic side effects - 0

Abnormal Laboratory Tests

Decreased Hgb	- 1
Decreased Hct	- 1
Decreased WBCs	- 1
Decreased neutrophils	- 1
Increased eosinophils	- 1
Increased SGOT	- 6
Increased SGPT	- 1
Increased GGT	- 2

Special Parameters

Sulbactam and ampicillin peak serum concentrations were determined on blood samples collected from 5 patients on days 1 and 5 of intramuscular drug administration.
Sulbactam peak serum concentrations were between 2.2 mcg/ml on day 1 at 1.0 hour following injection and 13.4 mcg/ml on day 5 at 0.5 hours after injection.
Ampicillin peak concentrations were between 2.6 mcg/ml on day 1 at 0.5 hours and 12.2 mcg/ml on day 5 at 0.5 hours.

3- Study #20-1

Title: A Noncomparative Study of Parenteral Sulbactam Sodium and Ampicillin Coadministered in Clinical Infections

Investigators:

Ronald Lee Nichols, M.D., F.A.C.S., Tulane University School of Medicine
William J. Mogabgab, M.D., Department of Infectious Diseases, Tulane University School of Medicine

Study Design:

Open, noncomparative study to determine the efficacy and safety of parenteral sulbactam sodium coadministered with ampicillin in the treatment of various clinical infections.

Patients:
A total of 84 patients were entered in this study.

Demographic Summary of All Patients

Age (years)

Range -	17-79
Mean -	38.56

Sex	
Male -	55 patients
Female -	29 patients

Dose and Route of Administration
Sulbactam sodium and ampicillin sodium were administered by intravenous infusion every six hours in the following ratios of sulbactam to ampicillin:

500 : 500	- 56 patients
500 : 1000	- 21 patients
1000 : 1000	- 7 patients

Duration of Therapy

Days		No. of Patients
1	-	1
2 - 3	-	9
4 - 5	-	30
6 - 7	-	17
8 -10	-	17
11 -15	-	8
19 -21	-	2

EVALUATION

EFFICACY
No. of Cases Evaluable - 66
No. of Cases Unevaluable - 18

Reasons Cases Unevaluable

No pre-treatment pathogen	- 8
No pre-treatment culture	- 1
Resistant organism isolated	- 2
No susceptibility testing done	- 2
Early discontinuation of treatment due to side effects	- 1
Inadequate duration of treatment	- 1
No follow-up	- 3

RESULT

INFECTION SKIN & SKIN STRUCTURE	No.	CLINICAL RESPONSE CURE	IMPROVE	FAIL
Cellulits	35	26	6	3
Abscess	23	16	6	1
Wound infection	4	2	2	-
Infected ulcer	1	1	-	-
Gangrene	3	-	2	1
Total	66	45 (68%)	16 (24%)	5 (8%)

AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
Bacillus spp.	2	2 (100%)	-
S. aureus	5	5 (100%)	-
S. pyogenes	16	16 (100%)	-
Streptococcus spp.	6	5 (83%)	1 (17%)
Streptococcus (Group D)	7	7 (100%)	-
S. faecalis	6	5 (83%)	1 (17%)
H. parainfluenzae	1	1 (100%)	-
E. coli	4	3 (75%)	1 (25%)
P. mirabilis	2	2 (100%)	-
A. calcoaceticus	1	1 (100%)	-
Citrobacter spp.	1	1 (100%)	-
Peptococcus spp.	1	1 (100%)	-
Bacteroides spp.	1	1 (100%)	-
B. melaninogenicus	1	1 (100%)	-
AMPICILLIN-RESISTANT ORGANISMS			
S. aureus	37	34 (92%)	3 (8%)
S. epidermidis	1	1 (100%)	-
E. coli	2	2 (100%)	-
P. mirabilis	2	1 (50%)	1 (50%)
P. vulgaris	2	2 (100%)	-
K. pneumoniae	1	1 (100%)	-
K. ozaenae	2	2 (100%)	-
Klebsiella spp.	1	1 (100%)	-
Providence spp.	1	1 (100%)	-
E. cloacae	2	2 (100%)	-
A. calcoaceticus	2	2 (100%)	-
C. diversus	1	1 (100%)	-
C. freundii	1	1 (100%)	
A. hydrophilia	1	1 (100%)	
S. liquefaciens	1	1 (100%)	

Five of the 66 evaluable patients developed a superinfection.

SAFETY

No. of patients evaluable - 84
No. of patients with local side effects - 0
No. of patients with systemic side efficets - 1 (1.2%)

SIDE EFFECTS
Tightness in throat and
substernal pain - 1 patient (1.2%)

Treatment was discontinued in this patient after the fifth dose.

Abnormal Laboratory Tests

Decreased Hct	- 2
Decreased neutrophils	- 1
Increased eospinophils	- 4
Decreased serum albumin	- 2
Increased SGOT	- 8
Increased SGPT	- 4
Increased LDH	- 9
Increased alkaline phosphatase	- 7
Increased GGT	- 1

4- Study #12-2
Title: An Open Study of Parenteral Sulbactam Sodium/Ampicillin

Investigator: Charles V. Sanders, M.D., Louisiana State University School of Medicine

Study Design:
Open noncomparative study to determine the efficacy and safety of parenteral sulbactam sodium combined with ampicillin in the treatment of patients with skin and skin structure, urinary tract and lower respiratory tract infections.

Patients
A total of 18 patients were entered in this study

Demographic Summary of All Patients

Age (years)		
Range	-	22-74
Mean	-	42.39
Sex		
Male	-	8
Female	-	0

Dose and Route of Administration
Sulbactam sodium and ampicillin sodium were administered by intravenous infusion every six hours in the following ratios of sulbactam to ampicillin:

500 :	500	- 9 patients
1000 :	1000	- 5 patients
1000 :	2000	- 4 patients

Duration of Therapy

Days	No. of Patients
1	1
2 - 3	4
4 - 5	3
6 - 7	4
8 -10	5
11	1

EVALUATION

EFFICACY
No. of Cases Evaluable - 11
No. of Cases Unevaluable - 7

Reasons Cases Unevaluble
No pre-treatment pathogen - 2
No susceptibility tesing done - 1
Colony count less than 10^5 - 2
Inadequate duration of treatment - 1
Addition of new antibiotic for intercurrent infection - 7

RESULTS

INFECTIONS		CLINICAL RESPONSE		
SKIN & SKIN STRUCTURE	No.	CURE	IMPROVE	FAIL
Cellulitis	5	2 (40%)	2 (40%)	1 (20%)
LOWER RESPIRATORY				
Bronchitis	1	-	1 (100%)	
Pneumonia	4	4 (100%)	-	
Total	5	4 (80%)	1 (20%)	
URINARY TRACT (Uncomp)				
Pyelonephritis	1		1 (100%)	

SKIN & SKIN STRUCTURE AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
Streptococcus spp.	1	1 (100%)	-
S. pyogenes	4	4 (100%)	-
E. coli	2	2 (100%)	-
A. calcoaceticus	1	1 (100%)	-
AMPICILLIN-RESISTANT ORGANISMS			
S. aureus	3	3 (100%)	-
Staphylococcus sp.*	1	1 (100%)	-

LOWER RESPIRATORY AMPICILLIN-SENSITIVE ORGANISMS	No.	ERADICATED	NOT ERADICATED
S. pneumoniae	3	3 (100%)	-
Streptococcus spp.	1	1 (100%)	-
H. influenzae	3	3 (100%)	-
H. parainfluenzae	1	1 (100%)	-
AMPICILLIN-RESISTANT ORGANISMS			
A. calcoaceticus	1	1 (100%)	
URINARY TRACT (Uncomp) AMPICILLIN-RESISTANT ORGANISM			
E. coli	1		1 (100%)

SAFETY
No. of patients evaluable - 18
No. of patients with local side effects - 1 (5.6%)
No. of patients with systemic side effects - 1 (5.6%)

SIDE EFFECTS
LOCAL
Thrombophlebitis - 1 case (5.6%)

SYSTEMIC
Itching - 1 case (5.6%)

Abnormal Laboratory Tests
Decreased Hgb - 2
Decreased Hct - 3
Decreased RBCs - 2
Decreased WBCs - 1
Decreased neutrophils - 1
Increased eosinophils - 1
Increased SGOT - 4
Increased LDH - 1
Increased alk. phosphatase - 1

5- Study #16-1
Title: A Noncomparative Study of Parenteral Sulbactam Sodium and Ampicillin Coadministered in Clinical Infections

Investigator: Nicholas V. Christou, M.D., Ph.D., Royal Victoria Hospital, Montreal, Quebec, Cananda

Study Design:
Open, noncomparative study to determine the efficacy and safety of sulbactam sodium combined with ampicillin in the treatment of a variety of clinical infections potentially resistant to ampicillin due to beta lactamase production.

Patients
A total of 37 patients were entered in this study.

Demographic Summary of All Patients

Age (years)		
Range	-	22-80
Mean	-	62.97

Sex		
Male	-	24
Female	-	13

Dose and Route of Administration

Sulbactam sodium and ampicillin sodium were administered by intravenous infusion every six hours in the following ratios of sulbactam to ampicillin:

500 : 500 - 3 patients
500 : 1000 - 34 patients

Duration of Therapy

Days		No. of Patients
2 - 3	-	6
4 - 5	-	1
6 - 7	-	6
8 -10	-	17
11 -14	-	4
15 -21	-	3

EVALUATION

EFFICACY

No. of Cases Evaluable - 3
No. of Cases Unevaluable - 34

Reasons Cases Unevaluble

No pre-treatment pathogen	- 8
No pre-treatment culture	- 11
Organism not identified	- 2
Resistant organism isolated	- 2
No susceptibility testing done	- 10
Inadequate cultures	- 1

RESULTS

INFECTIONS		CLINICAL RESPONSE	
SKIN & SKIN STRUCTURE	No.	CURE	IMPROVE
Cellulitis	1	1 (100%)	-
LOWER RESPIRATORY			
Pneumonia	1	1 (100%)	-
INTRA-ABDOMINAL			
Peritonitis	1	-	1 (100%)

SKIN & SKIN STRUCTURE AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
S. pyogenes	1	1 (100%)

LOWER RESPIRATORY AMPICILLIN-RESISTANT ORGANISMS		
E. coli	1	1 (100%)

INTRA-ABDOMINAL AMPICILLIN-SENSITIVE ORGANISM		
Streptococcus spp.	1	1 (100%)
K. oxytoca	1	1 (100%)

SAFETY

No. of Patients Evaluable - 37
No. of Patients with Local Side Effects - 0
No. of Patients with Systemic Side Effects - 0

Abnormal Laboratory Tests

Decreased Hgb	- 4
Decreased Hct	- 3
Increased platelets	- 8
Increased basophils	- 1
Decreased lymphocytes	- 1
Increased monocytes	- 1
Increased bilirubin	- 2
Decreased total proteins	- 4
Decreased serum albumin	- 6
Increased SGOT	- 8
Increased SGPT	- 11
Increased LDH	- 8
Increased alk. phosphatase	- 13
Increased BUN	- 3
Increased creatinine	- 1
Increased uric acid	- 2

6- Study #17-1

Title: A Therapeutic Trial of Epiglottitis (A Non Comparative Study of Parenteral Sulbactam Sodium in Combination with Ampicillin Sodium)

Investigator: Ellen Wald, M.D. and Charles D. Bluestone, M.D., Children's Hospital of Pittsburgh

Study Design:

Open, noncomparative study designed to asses efficacy and safety of sulbactam sodium coadministered with ampicillin in the treatment of epiglottitis caused by H. influenzae. Prior to the initiation of treatment, cultures were obtained from the blood and/or the surface of the epiglottis.

Patients
A total of 26 patients were entered in this study.

Demographic Summary of All Patients

Age (years)

Range:	1 - 2 years	-	11 patients
	3 - 4 years	-	9 patients
	5 - 7 years	-	6 patients

Mean: 3.12 years

Sex
Male: 19
Female: 7

Dose and Route of Administration
Sulbactam was coadministered with ampicillin by intravenous bolus injection (10 patients) or intravenous infusion (16 patients) every six hours.
Sulbactam was given at a dose of 30 mg /kg/day and ampicillin at 200 mg/kg/day.

Once the patients were significantly improved, the treatment was changed to either ampicillin alone (if the organisms was sensitive) or to cefaclor (if it was resistant).
Before the treatment was changed, a blood culture was obtained to assess the efficacy of sulbactam/ampicillin.

Duration of Sulbactam/Ampicillin Therapy

Days		No. of Patients
1	-	- 1
2 - 3	-	- 22
4 - 5	-	- 3

EVALUATION

EFFICACY
No. of Cases Evaluable: 19
No. of Cases Unevaluable: 7

Reasons Cases Unevaluable

No pre-treatment pathogen	- 2
Organism isolated not H. influenzae	- 1
No culture taken before changing therapy	- 3
Treatment given for only 1 day	- 1

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE
Epiglottitis	19	19 (100%)

AMPICILLIN-SENSITIVE ORGANISM	No.	BACTERIOLOGIC RESPONSE ERADICATED
H. influenzae	13	13 (100%)

AMPICILLIN-RESISTANT ORAGNISM		
H. influenzae	6	6 (100%)

SAFETY

No systemic or local side effects related to sulbactam/ampicillin therapy were reported.

Abnormal Laboratory Tests	
Decreased Hgb	- 1
Decreased Hct	- 2
Decreased RBCs	- 2
Increased alk. phosphatase	- 1
Increased SGOT	- 1
Increased SGPT	- 1

7- Study #14-1

Title: A Non comparative study of Parenteral Sulbactam/Ampicillin Coadministered in Gynecologic Infections

Investigators: Lauri D. Thrupp, M.D. and R. David Miller, M.D., University of California, Irvine

Study Design

This was an open, noncomparative study to assess the efficacy and safety of a 1:2 ratio of sulbactam/ampicillin in the treatment of patients with gynecologic infections.
Endometrial cultures were taken in every patient prior to initiation of treatment.

Patients

A total of 45 patients, 44 with acute endometritis and one with acute pyelonephritis, were entered in this study.

Demographic Summary of All Patients

Age (years)

Range : 5-40
Mean : 24.38

Sex

Female: 45

Dose and Route of Administration

Sulbactam 1.0 g and ampicillin 2.0 g were coadministered by intravenous infusion every six hours to all 45 patients.
At the discretion of the investigator, treatment was changed to oral ampicillin in 29 patients, parenteral ampicillin/gentamicin in 4 patients, parenteral ampicillin and chloromycetin in 1 patient, parenteral gentamicin/clindamycin in 3 patients and parenteral ampicillin/gentamicin/clindamycin in 7 patients.

Duration of Sulbactam/Ampicillin Therapy

Days	No. of Patients
1	5
2 - 3	30
4 - 5	10

EVALUATION

EFFICACY
No. of Cases Evaluable - 0
No. of Cases Unevaluable - 45

Reason Cases Unevaluable
No pre-treatment pathogen - 4
Resistant organism isolated - 3
Inadequate duration of therapy - 5
Concomitant effective antibiotic - 2
No post-treatment culture - 31

In addition, susceptibility studies were performed in only 13 of the 86 bacterial isolates cultured pre-treatment.

SAFETY
Total No. of Patients: 45
No. of Patients with Local Side Effects: 1 (2%)
No. of Patients with Systemic Side Effects: 2 (4%)

SIDE EFFECTS
LOCAL
Thrombophlebitis - 1 (2%)

Systemic
Diarrhea - 1 (2%)
Rash - 1 (2%)

Abnormal Laboratory Tests
There were no abnormal values which "may be related" to sulbactam/ampicillin therapy.

8- Study #98-2
Title: An Open Study of the Efficacy and Safety of Sulbactam/Ampicillin Administered Parenterally and Sultamicillin Administered Orally in Childhood Skeletal Infections

Investigator: Stephen C. Aronoff, M.D., Rainbow Babies and Children's Hospital, Cleveland, OH

Study Design
This was an open, noncomparative study to determine the efficacy and safety of a 1:4 ratio of sulbactam and ampicillin administered intravenously to children with septic arthritis or osteomyelitis. Patients demonstrating clinical improvement were then treated with oral sultamicillin, an ester of ampicillin which on absorption yields equimolar concentrations of ampicillin and sulbactam.

Appropriate cultures were taken before initiation of therapy and at the time parenteral treatment was switched to oral treatment.

Patients
A total of 4 patients were entered in this study.

Demographic Summary
Age
8 months and 16 months - 2 patients
7 years and 8 years - 2 patients

Sex
Male - 3 patients
Female - 1 patient

Dose and Route of Administration
Sulbactam and ampicillin were administered by intravenous infusion in doses of 50 mg/kg/day and 200 mg/kg/day, respectively, in equally divided doses every six hours. Sultamicillin was administered orally at a dosage of 50 mg/kg/day in two equally divided doses.

Duration of Therapy

	Sulbactam/Ampicillin	Sultamicillin
Days	5	22 - 24

EVALUATION

EFFICACY
No. of Cases Evaluable: 1
No. of Cases Unevalulble: 3

Reasons Cases Unevaluable
No pre-treatment pathogen - 3 cases

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE
Septic arthritis	1	1 (100%)

AMPICILLIN-SENSITIVE ORGANISM		BACTERIOLOGIC RESPONSE ERADICATED
H. influenzae type B	1	1 (100%)

SAFETY
There were no adverse reactions during sulbactam/ampicillin parenteral treatment.
After several days of oral sultamicillin therapy, two patients developed moderate diarrhea, and one experienced loose stools.

ABNORMAL LABORATORY TESTS
There were no abnormal values reported.

Summary of Open, Noncomparative Studies
(Domestic and Canadian)

No. of Studies: Domestic - 7
Canadian - 1

No. of Investigators: 11

	Adults	Children	Total
No. of Patients	229	30	259

	Adults	Children
Age Range	15 -80	8 months - 1
		1 - 2 years - 12
		3 - 4 years - 9
		5 - 8 years - 8

Sex
Male - 137
Female - 122

Dose (Sulbactam : Ampicillin)

Adults	No.	Children	No.
500 : 500 q 6 h	101	Sulbactam - 30 mg/kg/day Ampicillin - 200 mg/kg/day	26
500 : 1000 q 6 h	62		
500 : 1500 q 6 h	1		
1000 : 1000 q 6 h	12	Sulbactam - 50 mg/kg/day Ampicillin-200 mg/kg/day	4
500 : 2000 q 6 h	4		
1000 : 2000 q 6 h	49		

Route of Administration	Adults	Children
IV infusion	224	20
IV injection	-	10
IM injection	5	-

EFFICACY EVALUATION
ADULTS: No. of Cases Evaluable - 113

INFECTIONS		CLINICAL RESPONSE		
SKIN & SKIN STRUCTURE	No.	CURE	IMPROVE	FAIL
Cellulitis	58	44 (75.9%)	10 (17.2%)	4 (6.9%)
Abscess	32	23 (71.9%)	8 (25.0%)	1 (3.1%)
Ulcers	3	1 (33.3%)	2 (66.7%)	-
Wound infection	5	3 (60.0%)	2 (40.0%)	-
Gangrene	3	-	2 (66.7%)	1 (33.3%)
Total	101	71 (70.3%)	24 (23.8%)	6 (5.9%)

LOWER RESPIRATORY	No.	CURE	IMPROVE
Bronchitis	2	1 (50.0%)	1 (50.0%)
Pneumonia	7	6 (85.7%)	1 (14.3%)
Total	9	7 (77.8%)	2 (22.2%)
UNCOMPLICATED UTI	2		2 (100%)
INTRA-ABDOMINAL			
Peritonitis	1		1 (100%)

SKIN & SKIN STRUCTURE
AMPICILLIN-SENSITIVE

ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
Bacillus sp.	2	2 (100%)	
S. aureus	6	6 (100%)	
S. epidermidis	1	1 (100%)	
S. pyogenes	28	28 (100%)	
S. viridans	1	1 (100%)	
Streptococcus sp.	9	8 (88.9%)	1 (11.1%)
Group D streptococcus	7	7 (100%)	
S. faecalis	6	5 (83.3%)	1 (16.7%)
H. parainfluenzae	1	1 (100%)	
P. mirabilis	4	4 (100%)	
E. coli	7	6 (85.7%)	1 (14.3%)
E. cloacae	2	2 (100%)	
A. calcoaceticus	2	2 (100%)	
Citrobacter sp.	1	1 (100%)	
Salmonella type B	1	1 (100%)	
Peptococcus sp.	3	3 (100%)	
Bacteroides sp.	1	1 (100%)	
B. melaninogenicus	1	1 (100%)	

SKIN & SKIN STRUCTURE
AMPICILLIN-RESISTANT

ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
S. aureus	49	46 (93.9%)	3 (6.1%)
S. epidermidis	2	2 (100%)	
Staphylococcus sp.	2	2 (100%)	
S. liquefaciens	1	1 (100%)	
E. coli	3	2 (66.7%)	1 (33.3%)
P. mirabilis	3	2 (66.7%)	1 (33.3%)
P. vulgaris	2	2 (100%)	
Providencia sp.	1	1 (100%)	
Enterobacter sp.	1	1 (100%)	
E. cloacae	2	2 (100%)	
A. calcoaceticus	2	2 (100%)	
C. diversus	1	1 (100%)	
C. freundii	1	1 (100%)	
Klebsiella sp.	1	1 (100%)	
K. pneumoniae	2	2 (100%)	
K. ozaenae	2	2 (100%)	
A. hydrophilia	1	1 (100%)	

LOWER RESPIRATORY
AMPICILLIN-SENSITIVE

ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
Streptococcus sp.	1	1 (100%)	
S. pneumoniae	3	3 (100%)	
H. influenzae	4	4 (100%)	
H. parainfluenzae	1	1 (100%)	

LOWER RESPIRATORY
AMPICILLIN-RESISTANT

ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
H. influenzae	2	2 (100%)	
E. coli	1	1 (100%)	
A. calcoaceticus	1	1 (100%)	

UNCOMPLICATED UTI
AMPICILLIN-SENSITIVE

ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
E. coli	1	1 (100%)	

UNCOMPLICATED UTI
AMPICILLIN-RESISTANT

ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
E. coli	1		1 (100%)

INTRA-ABDOMINAL
AMPICILLIN-SENSITIVE

ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
Streptococcus sp.	1	1 (100%)	
K. oxytoca	1	1 (100%)	

EFFICACY EVALUATION
CHILDREN: No. of Cases Evaluble - 20

INFECTIONS UPPER RESPIRATORY	No.	CLINICAL RESPONSE CURE
Epiglottitis	19	19 (100%)
BONE/JOINT		
Septic arthritis	1	1 (100%)

UPPER RESPIRATORY AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
H. influenzae	13	13 (100%)

UPPER RESPIRATORY AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
H. influenzae	6	6 (100%)

BONE/JOINT AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
H. influenzae	1	1 (100%)

SAFETY EVALUATION

	ADULTS	CHILDREN	TOTAL
No. of Patients	229	30	259
No. with Local Side Effects	2 (0.9%)	0	2 (0.8%)
No. with Systemic Side Effects	6 (2.6%)	0	6 (2.3%)
LOCAL SIDE EFFECTS			
Thrombophlebitis	2 (0.9%)		2 (0.8%)
SYSTEMIC SIDE EFFECTS			
Abdominal distention	1 (0.4%)		1 (0.4%)
Diarrhea	1 (0.4%)		1 (0.4%)
Rash	2 (0.9%)		2 (0.9%)
Itching	1 (0.4%)		1 (0.4%)
Tightness in throat and substernal pain	1 (0.4%)		1 (0.4%)

ABNORMAL LABORATORY TESTS	ADULTS	CHILDREN	TOTAL
Decreased Hgb	6	1	7
Decreased Hct	9	2	11
Decreased RBCs	3	2	5
Decreased WBCs	1	0	1
Decreased neutrophils	2	0	2
Decreased lymphocytes	1	0	1
Increased platelets	8	0	8
Increased eosinophils	10	0	10
Increased monocytes	1	0	1
Increased basophils	2	0	2
Decreased serum albumin	8	0	8
Decreased total proteins	4	0	4
Increased SGOT	21	1	22
Increased SGPT	15	1	16
Increased LDH	18	0	18
Increased alk. phosphatase	21	1	22
Increased bilirubin	2	0	2
Increased GGT	2	0	2
Increased BUN	3	0	3
Increased creatinine	1	0	1
Increased uric acid	2	0	2
Urine hyaline casts	1	0	1

Conclusions:

These open, non-comparative studies were conducted to determine the efficacy and safety of sulbactam plus ampicillin in the treatment of patients with infections caused by pathogenic bacteria susceptible to the combination treatment regimen. A total of 259 patients, 229 adults and 30 children, were enrolled in these studies.
Evaluation of drug efficacy was assessed in 113 adults and in 20 children. All patients were considered in assessing drug safety.

In adult patients, a satisfactory clinical response (cure/improve) was achieved in 95/101 (94%) patients with skin and skin structure infections, in 9/9 (100%) with lower respiratory infections, in 2/2 (100%) urinary tract infections and in 1/1 (100%) with peritonitis.

In patients with skin and skin structure infections, sulbactam/ampicillin eradicated 80/83 (96%) ampicillin-sensitive organisms and 71/76 (93%) ampicillin-resistant organisms; in lower respiratory infections eradicated 9/9 (100%) ampicillin-sensitive organisms and 4/4 (100%) ampicillin-resistant organisms, in urinary tract infections eradicated 1/1 (100%) ampicillin-sensitive organsism and 0/1 (100%) ampicillin-resistant organism, and in one patient with peritonitis eradicated 2/2 (100%) ampicillin-sensitive organisms.

In children, a satisfactory clinical response was achieved in 19/19 (100%) patients with epiglottitis and in 1/1 (100%) patient with septic arthritis.

In patients with epiglottitis, sulbactam/ampicillin eradicated 13/13 (100%) ampicillin-sensitive _H. influenzae_ and 6/6 (100%) ampicillin-resistant _H. influenzae_. In the patient with septic arthritis, an ampicillin-sensitive _H. influenzae_ was eradicated.

In adults, local side effects (thromblophlebitis) were reported in 2/224 (0.9%) patients who were treated intravenously. No local side effects were reported in 5 adults treated intramuscularly or in any of the 30 children treated intravenously.
Systemic side effects were reported in 6/229 (2.6%) adults. No systemic side effects were reported in children.

The most commonly reported abnormal laboratory tests were decreases in Hgb and Hct, increased platelet counts, eosinophilia and increased liver function test values.

EUROPEAN STUDIES

I. Controlled Studies

1- Protocol 33-2
Title: An Open, Comparative Study of the Efficacy of Sulbactam Plus Ampicillin Versus Gentamicin Plus Metronidazole in the Management of Intra-Abdominal Sepsis.

Investigator: Mr. J. P. Duignan, MSc, FRCS, Mater Misericordiae Hospital, Dublin, Eire

Study Design
An Open randomized comparative study to determine the efficacy and safety of sulbactam plus ampicillin as compared with gentamicin plus metronidazole in the management of intra-abdominal infections.

Patients
A total of 40 patients were enrolled in this study; twenty were randomized to the sulbactam/ampicillin group and 20 to the gentamicin/metronidazole group.

Demographic Summary

Age (years)	Sulbactam/Ampicillin	Gentamicin/Metronidazole
Range	13-89	13-86
Mean	38.5	42.9
Sex		
Male	12	14
Female	8	6

Dose and Route of Administration
Patients in the sulbactam/ampicillin group received sulbactam (4g daily; 1.0 g qid) in a 1:1 combination with ampicillin administered by intravenous injection. The control group received gentamicin (240 mg daily; 80 mg tid) plus metronidazole (1.5 g daily; 500 tid) by the intravenous route.

Duration of Therapy

Days	Sulbactam/Ampicillin	Gentamicin/Metronidazole
Range	1-8	3-10
Mean	6.2	6.7

EVALUATION

EFFICACY

Sulbactam/Ampicillin Group
No. of Cases Evaluable - 0
No. of Cases Unevaluable - 20

Reason Cases Unevaluable

No pre-treatment pathogen	- 6
Patient refused further treatment after 2 days	- 1
Patient died on day 1 of treatment	- 1
No susceptibility testing done	- 11

In addition, the investigator did not make an assessment of the patient's outcome in any of the cases.

Gentamicin/Metronidazole Group
Since none of the cases in the sulbactam/ampicillin group were evaluable, there is no need to evaluate the efficacy in the control group. Here again, the investigator made no assessmsne of the outcome in any of these patients.

SAFETY
Sulbactam/Ampicillin Group

No. of Patients	- 20
No. with Local Side Effects	- 4 (20%)
No. with Systemic Side Effects	- 0

LOCAL SIDE EFFECTS

Pain at I.V. injections site	- 2 (10%)
Thrombophlebitis	- 2 (10%)

Gentamicin/Metronidazole Group

No. of Patients	- 20
No. with Local Side Effects	- 7 (35%)
No. with Systemic Side Effects	- 1 (5%)

LOCAL SIDE EFFECTS
Pain at I.V. injections site - 7 (35%)

SYSTEMIC SIDE EFFECT
Tinnitus - 1 (5%)

Deaths
Sulbactam/Ampicillin Group
One patient died on day 1 of treatment from massive thrombosis of the small bowel.

Gentamicin/Metronidazole Group
Three patients died during the course of the trial. One died as a result of surgical problems leading to an intra-abdominal abcess.
One died from hepato-renal failure developing on pre-existing portal fibrosis. The third patient with a perforation of the duodenum developed hemorrhagic pancreatitis and died in renal failure.

ABNORMAL LABORATORY TESTS

Sulbactam/Ampicillin Group

Increased platelets	- 2
Increased AST	- 1
Increased ALT	- 3

Gentamicin/Metronidazol Group

Increased platelets	- 3
Decreased platelets	- 1
Increased AST	- 3
Increased ALT	- 3
Increased eosinophils	- 1
Increased serum urea	- 1
Increased creatinine	- 1

Conclusions:
This study is not valid for the evaluation of comparative efficacy since there were no evaluable cases in the sulbactam ampicillin group.

The incidence of local side effects was higher in the gentamicin/metronidazole group, and the only systemic side effect reported (tinnitus) also occurred in this group.

2- Protocol #84-1
Title: An Open, Comparative Study of the Combination of Sulbactam with Ampicillin Versus Cefotaxime in Serious Acute Bone and Joint Infections and Skin and Skin Structure Infections.

Investigators: Professor Keyl and Dr. Pfister, Orthopedic Clinic, University of Munich, Munich, Germany

Study Design:
An open, randomized, comparative study to determine the efficacy and safety of sulbactam plus ampicillin as compared with cefotaxime in the treatment of bone and joint infections and skin and skin structure infections caused by pathogens potentially resistant to ampicillin.

Patients
A total of 23 patients were enrolled in this study; thirteen were randomized to the sulbactam/ampicillin group and 10 to the cefotaxime group.

Demographic Summary

Age (years)	Sulbactam/Ampicillin	Cefotaxime
Range	20-75	13-71
Mean	46.5	51.8
Sex		
Male	8	3
Female	5	7

Dose and Route of Administration

Patients in the sulbactam/ampicillin group received sulbactam (3.0 g daily; 1.0 g tid) plus ampicillin (6.0 daily; 2.0 g tid) by intravenous infusions.

Patients in the control group received cefotaxime (6.0 g daily; 2.0 g tid) also by intravenous infusions.

Duration of Therapy Days	Sulbactam/Ampicillin	Cefotaxime
Range	8-16	2-16
Mean	13.9	12.4

EVALUATION

EFFICACY

	Sulbactam/Ampicillin	Cefotaxime
No. of Cases Evaluable	7	5
No. of Cases Unevaluable	6	5

Reasons Cases Unevaluable		
No pre-treatment pathogen	- 2	1
No x-Rays to confirm diagnosis	- 4	3
Resistant organisms isolated	- 0	1

RESULTS

INFECTION	SULBACTAM/AMPICILLIN CLINICAL RESPONSE			CEFOTAXIME CLINICAL RESPONSE		
BONE/JOINT	No.	CURE	IMPROVE	No.	CURE	IMPROVE
Septic arthrits	4	1 (25%)	3 (75%)	4	1 (25%)	3 (75%)
SKIN & SKIN STRUCTURE						
Ulcer	1		1 (100%)	1		1 (100%)
Abscess	2	2 (100%)				
Total	3	2 (66.7%)	1 (33.3%)			

BONE/JOINT	SULBACTAM/AMPICILLIN BACTERIOLOGIC RESPONSE			CEFOTAXIME BACTERIOLOGIC RESPONSE		
AMPICILLIN-SENSITIVE ORGANISMS	No.	ERADICATED	NOT ERAD	No.	ERADICATED	NOT ERAD
S. faecalis	1	1 (100%)		1		1 (100%)
S. aureus	-			3	2 (66.7%)	1 (33.3%)
AMPICILLIN-RESISTANT ORGANISMS						
S. aureus	3	2 (66.7%)	1 (33.3%)	1	1 (100%)	
S. epidermidis	1	1 (100%)				

Table continued

SKIN & SKIN STRUCTURE AMPICILLIN-SENSITIVE ORGANISMS	SULBACTAM/AMPICILLIN No.	SULBACTAM/AMPICILLIN BACTERIOLOGIC RESPONSE ERADICATED	CEFOTAXIME No.	CEFOTAXIME BACTERIOLOGIC RESPONSE ERADICATED
E. coli	1	1 (100%)		
P. mirabilis	1	1 (100%)		
S. faecalis	1	1 (100%)		
AMPICILLIN-RESISTANT ORGANISMS				
S. aureus	2	2 (100%)	1	1 (100%)

Colonization with a resistant P. aeruginosa occurred in one patient with a skin and skin structure infection in the sulbactam/ampicillin group. In the cefotaxime group, one patient with an abscess caused by a resistant S. aureus had a relapsed one week after treatment was discontinued.

SAFETY

Sulbactam/Ampicillin Group
No. of Patients - 13
No. with Local Side Effects - 0
No. with Systemic Side Effects - 6 (46.2%)

SYSTEMIC SIDE EFFECTS

Nausea	- 1 (7.7%)
Diarrhea	- 1 (7.7%)
Oral candidiasis	- 1 (7.7%)
Vaginal candidiasis	- 1 (7.7%)
Rash	- 2 (15.4%)

Cefotaxime Group
No. of Patients - 10
No. with Local Side Effects - 0
No. with Systemic Side Effects - 1 (10%)

SYSTEMIC SIDE EFFECT
Itching - 1 (10%)

ABNORMAL LABORATORY TESTS

Sulbactam/Ampicillin Group
Decreased Hgb - 2
Decreased Hct - 2
Decreased RBCs - 2
Increased AST - 1
Increased ALT - 1

Cefotaxime Group
Decreased Hgb - 1
Decreased Hct - 1
Decreased RBCs - 1
Increased eosinophils - 1
Increased AST - 2
Increased ALT - 3
Increased alk. phosphatase - 3

Conclusions:
Sulbactam/ampicillin treatment was clinically effective in 4/4 (100%) patients with septic arthritis and in 3/3 (100%) with skin and skin structure infections. Cefotaxime treatment was clinically effective in 4/4 (100%) patients with septic arthritis and in 1/1 (100%) with a skin structure infection.

In patients with septic arthritis, sulbactam/ampicillin eradicated 1/1 (100%) ampicillin-sensitive organism and 3/4 (75%) ampicillin-resistant organisms.
In patients with skin and skin structure infections, sulbactam/ampicillin eradicated 3/3 (100%) ampicillin-sensitive organisms and 2/2 (100%) ampicillin -resistant organisms.
In patients with septic arthritis, cefotaxime eradicated 2/4 (50%) ampicillin-sensitive organisms and 1/1 (100%) ampicillin-resistant organisms.
In one patient with a skin and skin structure infections, cefotaxime eradicated 1/1 (100%) ampicilllin-resistant organism.

Systemic side effects were significantly higher in the sulbactam/ampicillin group than in the cefotaxime group.

The number of patients in each treatment group is too small to allow for an adequate comparative evaluation of the efficacy and safety between the two drugs.

3- Protocol B

Title: A Third Party Blinded Multicenter Comparative Study of Parenteral Sulbacatam/Ampicillin Versus Metronidazole/Gentamicin Coadministered in Cases of Anaerobic and Polymicrobic Infections.

Investigators:
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Study Design
A third party blinded, randomized, comparative trial of the efficacy and safety of sulbactam/ampicillin versus metronidazole/gentamicin in the treatment of patients with suspected or documented anaerobic and polymicrobic infections.

Patients
A total of 46 patients were entered in this study; twenty-four were randomly assigned to the sulbactam/ampicillin group and 22 to the metronidazole/gentamicin group.

Demographic Summary	Sulbactam/Ampicillin	Metronidazole/Gentamicin
Age (years)		
Range	13-89	15-86
Mean	39.4	37.7
Sex		
Male	20	15
Female	4	7

Dose and Route of Administration
Patients in the sulbactam/ampicillin group received 1.0 g sulbactam and 2.0 g ampicillin administered as an intravenous infusion every six hours. Patients in the control group received a 15 mg/kg loading dose of metronidazole followed by 7.5 mg/kg every 6 hours by intravenous infusion with 1.5 mg/kg gentamicin by intravenous infusion every eight hours. To blind the eight hourly gentamicin administration, an equal volume of physiological saline was administered to patients assigned to the sulbactam/ampicillin combination.

Duration of Therapy Days	Sulbactam/Ampicillin	Metronidazole/Gentamicin
Range	2-12	4-9
Mean	5.6	5.9

EVALUATION

EFFICACY

	Sulbactam/Ampicillin	Metronidazole/Gentamicin
No. of Cases Evaluable	11	10
No. of Cases Unevaluable	13	12
Reasons Cases Unevaluable		
No pre-treatment pathogen	10	9
Resistant organism isolated	2	2
Patient died of CHF	1	-
No pre-treatment culture	-	1

RESULTS

INFECTION	SULBACTAM/AMPICILLIN				METRONIDAZOLE/GENTAMICIN			
		CLINICAL RESPONSE				CLINICAL RESPONSE		
INTRA-ABDOMINAL	No.	CURE	IMPROVE	FAIL	No.	CURE	IMPROVE	FAIL
Abscess	2	1(50%)		1(50%)	-			
Peritonitis	9	9(100%)			10	8(80%)	1(10%)	1(10%)
TOTAL	11	10(90.9%)		1(9.1%)	10	8(80%)	1(10%)	1(10%)

INTRA-ABDOMINAL AMPICILLIN-SENSITIVE ORGANISMS	SULBACTAM/AMPICILLIN BACTERIOLOGIC RESPONSE			CLINDAMYCIN/GENTAMICIN BACTERIOLOGIC RESPONSE		
	No.	ERADICATED	NOT ERAD	No.	ERADICATED	NOT ERAD
S. epidermidis	1	1 (100%)		1	1 (100%)	
Streptococcus sp.	2	2 (100%)		4	4 (100%)	
S. faecalis	1	1 (100%)		-		
Lactobacillus sp.	1	1 (100%)		-		
Peptococcus sp.	1	1 (100%)		1	1 (100%)	
Peptostreptococcus sp.	1	1 (100%)		1	1 (100%)	
Eubacterium sp.	3	3 (100%)		2	2 (100%)	
Bifidobacterium sp.	1	1 (100%)		-	-	
Propionibacterium sp.	1	1 (100%)		3	3 (100%)	
Fusobacterium sp.	-			2	2 (100%)	
Bacteroides sp.	-			2	2 (100%)	
B. fragilis	3	3 (100%)		-		
B. melaninogenicus	1	1 (100%)		-		
AMPICILLIN-RESISTANT ORGANISMS						
E. coli	10	10 (100%)		9	7 (77.8%)	2 (22.2%)
K. pneumoniae	1	1 (100%)		-		
Enterobacter sp.	1	1 (100%)		-		
C. freundii	1	1 (100%)		-		
P. aeruginosa	1	1 (100%)		-		
Clostridium sp.	1	1 (100%)		-		
Eubacterium sp.	1	1 (100%)		-		
Bacteroides sp.	4	4 (100%)		4	4 (100%)	
B. fragilis	[illegible]	8 (100%)		7	7 (100%)	
B. melaninogenicus	-			1	1 (100%)	
C. jejuni	-			1	1 (100%)	

One patient in the sulbactam/ampicillin group who had an inta-abdominal abscess developed a superinfection with a resistant <u>P. morganii</u> and a resistant <u>Enterobacter</u> species.

SAFETY

Sulbactam/Ampicillin Group

No. of Patients - 24
No. with Local Side Effects - 1 (4.2%)
No. with Systemic Side Effects - 2 (8.3%)

LOCAL SIDE EFFECTS

Thrombophlebitis - 1 (4.2%)

SYSTEMIC SIDE EFFECTS

Vomiting - 1 (4.2%)
Diarrhea - 2 (8.3%)

Metronidazole/Gentamicin Group

No. of Patients - 22
No. with Local Side Effects - 0
No. with Systemic Side Effects - 2(9%)

SYSTEMIC SIDE EFFECTS
Diarrhea - 1 (4.5%)
Rash - 1 (4.5%)

Deaths
One patient in the sulbactam/ampicillin group died on the fifth day of treatment of pneumonia and congestive heart failure. He was 85 years of age.

ABNORMAL LABORATORY TESTS

Sulbactam/Ampicillin Group
Increased SGOT - 1

Metronidazole/Gentamicin Group
Increased platelets - 1
Increased SGOT - 4

Conclusions:
Sulbactam/ampicillin treatment was clinically effective in 10/11 (91%) patients with intra-abdominal infections. Metronidazole/gentamicin treatment was clinically effective in 9/10 (90%) patients with intra-abdominal infections.

Sulbactam/ampicillin eradicated 16/16 (100%) ampicillin-sensitive organisms and 28/28 (100%) ampicillin-resistant organisms. Metronidazole/gentamicin eradicated 16/16 (100%) ampicillin-sensitive organisms and 20/22 (91%) ampicillin-resistant organisms.

Side effects were similar in both treatment groups.

Results of this study demonstrated that sulbactam/ampicillin is as safe and effective as metronidazole/gentamicin in the treatment of patients with intra-abdominal infections.

4- Protocol #29-4
Title: A Third Party Blinded Multicenter Comparative Study of Parenteral Sulbactam/Ampicillin Versus Clindamycin/Gentamicin Co-Administered in Cases of Intra-Abdominal Infections and Related Infections of the Gastro-Intestinal Tract

Investigators:
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Study Design
A third party blinded, randomized, comparative trial of the efficacy and safety of sulbactam/ampicillin and a clindamycin/gentamicin regimen in patients with intra-abdominal infections caused by anaerobic and polymicrobic infections.

Patients
A total of 80 patients were entered in this ongoing study. Forty patients were randomly assigned to the sulbactam/ampicillin group and 40 to the clindamycin/gentamicin group.

Demographic Summary

Age (years)	Sulbactam/Ampicillin	Clindamycin/Gentamicin
Range	19-81	18-94
Mean	52.2	53.9
Sex		
Male	24	22
Female	16	18

Dose and Route of Administration
Patients in the sulbactam ampicillin group received 1.0 g sulbactam and 2.0 g ampicillin administered as an intravenous infusion every six hours. Patients in the control group received 600 mg of clindamycin every 6 hours by intravenous infusion together with 1.5 mg/kg gentamicin by intravenous infusion every 8 hours.
To blind the eight hourly gentamicin administration, an equal volume of physiological saline was administered to patients assigned to the sulbactam/ampicillin combination.

Duration of Therapy

Days	Sulbactam/Ampicillin	Clindamycin/Gentamicin
Range	1-10	1-14
Mean	5.4	5.82

EVALUATION

EFFICACY

	Sulbactam/Ampicillin	Clindamycin/Gentamicin
No. of Cases Evaluable	24	17
No. of Cases Unevaluable	16	23
Reasons Case Unevaluable		
No pre-treatment pathogen	8	14
No evidence of infection	3	1
No susceptibility testing done	2	1
Resistant organisms isolated	-	1
Type of organism not specified	-	1
No follow-up	2	-
Concomitant antibiotic	-	1
Patient refused to continue treatment	-	1
Patient died during treatment	1	2
Treatment discontinued due to high creatinine (pre-treatment)	-	1

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RESULTS

INFECTION	SULBACTAM/AMPICILLIN CLINCAL RESPONSE				CLINDAMYCIN/GENTAMICN CLINICAL RESPONSE			
INTRA-ABDOMINAL	No.	CURE	IMPROVE	FAIL	No.	CURE	IMPROVE	FAIL
Peritonitis	21	17	3	1	12	10	2	
Abscess	3	2		1	5	4	1	
TOTAL	24	19(79.2%)	3 (12.5%)	2(8.3%)	17	14(82.4%)	3 (17.6%)	

AMPICILLIN-SENSITIVE ORGANISMS	BACTERIOLOGIC RESPONSE			BACTERIOLOGIC RESPONSE		
	No.	ERADICATED	NOT ERAD	No.	ERADICATED	NOT ERAD
Streptococcus sp.	4	3 (75%)	1 (25%)	1	1 (100%)	
S. viridans	3	3 (100%)		3	3 (100%)	
Group D strep	1	1 (100%)		-		
S. pyogenes	1	1 (100%)		-		
E. coli	4	4 (100%)		5	4 (80%)	1 (20%)
M. morganii	-			1	1 (100%)	
Enterobacter sp.	1	1 (100%)		-		
C. perfingens	-			1	1 (100%)	
Bacteroides sp.	-			1	1 (100%)	
B. fragilis	-			4	4 (100%)	
B. ruminicola	1		1 (100%)			
F. nucleatum	1	1 (100%)				

AMPICILLIN-RESISTANT ORGANISMS	SULBACTAM/AMPICILLIN BACTERIOLOGIC RESPONSE			CLINDAMYCIN/GENTAMICIN BACTERIOLOGIC RESPONSE		
	No.	ERADICATED	NOT ERAD	No.	ERADICATED	NOT ERAD
S. aureus	1	1 (100%)		-		
S. epidermidis	-			1	1 (100%)	
E. coli	14	12 (85.7%)	2 (14.3%)	10	6 (60%)	4 (40%)
Klebsiella sp.	3	2 (66.7%)	1 (33.3%)	-		
K. pneumoniae	1	1 (100%)		2	2 (100%)	
Enterobacter sp.	1	1 (100%)		-		
C. freundii	-			1	1 (100%)	
P. aeruginosa	-			1	1 (100%)	
Bacteroides sp.	5	5 (100%)		2	2 (100%)	
B. fragilis	7	7 (100%)		4	4 (100%)	
B. corrodens	1	1 (100%)				

SAFETY

Sulbactam/Ampicillin Group

No. of Patients - 40
No. with Local Side Effects - 3 (7.5%)
No. with Systemic Side Effects - 1 (2.5%)

LOCAL SIDE EFFECTS

Thrombophlebitis - 3 (7.5%)

SYSTEMIC SIDE EFFECT

Diarrhea - 1 (2.5%)

Clindamycin/Gentamicin Group

No. of Patients - 40
No. with Local Side Effects - 2 (5%)
No. with Systemic Side Effects - 3 (7.5%)

LOCAL SIDE EFFECTS
Thrombophlebitis - 2 (5%)

SYSTEMIC SIDE EFFECTS
Diarrhea - 2 (5%)
Urticaria - 1 (2.5%)

Deaths
One patient in the sulbactam/ampicillin group and two in the clindamycin/gentamicin group died during the study. None of the deaths was considered to be drug related.

Abnormal Laboratory Tests
Sulbactam/Ampicillin Group

Increased eosinophils	- 2
Increased bilirubin	- 2
Increased SGOT	- 4
Increased SGPT	- 6
Increased Alk. phosphatase	- 5

Clindamycin/Gentamicin Group

Increased eosinophils	- 2
Increased bilirubin	- 2
Increased SGOT	- 8
Increased SGPT	- 6
Increased alk. phosphatase	- 8
Increased BUN	- 1
Increased creatinine	- 3

Conclusions:
Sulbactam/ampicillin was clinically effective in 22/24 (92%) patients with intra-abdominal infections.
Clindamycin/gentamicin was clinically effective in 17/17 (100%) patients with intra-abdominal infections.

Sulbactam/ampicillin eradicated 14/16 (87.5%), ampicillin-sensitive organisms and 30/33 (91%) ampicillin-resistant organisms.
Clindamycin/gentamicin eradicated 15/16 (94%) ampicillin-sensitive organisms and 17/21 (81%) ampicillin-resistant organisms.

Local side effects were similar in both groups, and systemic side effects were somewhat higher in the clindamycin/gentamicin group.

Results of this study demonstrated that sulbactam/ampicillin is as safe and effective as clindamycin/gentamicin in the treatment of patients with intra-abdominal infections.

II. Uncontrolled Studies

1. Protocol # 27-1
Title: An Open Study to Assess the Safety, Toleration, Efficacy and Pharmacokinetics of Combination Parenteral Therapy with Sulbactam plus Ampicillin in Patients with Serious Infections of the Skin and Skin Structures and Ears, Nose and Throat

Investigator: Prof. Dr. P. Federspil, Universitats-Hals-Nasen und Ohrenklinik des Saarlandes, Hamburg, Germany

Study Design
Open, non-comparative

Patients
Fifteen adults patients were entered into this study.

Demographic Summary

Age (years)

Range: 20-80
Mean: 42

Sex

Male: 14
Female: 1

Dose and Route of Administration
The majority of the patients received multiple intravenous doses of sulbactam 500 mg tid in combination with ampicillin 2 g tid administered by intravenous infusion over 15-30 minutes (13 patients) or by intravenous injection (1 patients). In one patient the daily dose of sulbactam was 1 g (500 mg bid) and that of ampicillin 4 g (2 g bid) by intravenous infusion.

Duration of Therapy
The duration of therapy ranged from 1-20 days with a mean duration of 7.6 days.

EVALUATION

EFFICACY
No. of Cases Evaluable: 0
No. of Cases Unevaluable: 15

Reasons Cases Unevaluable
No pre-treatment pathogen: 2
No pre-treatment culture: 8
No post-treatment culture: 3
Treatment discontinued due to side effects: 2

SAFETY
No. of Patients: 15
No. with Local Side Effects: 0
No. with Systemic Side Effects: 3 (20%)

Side Effects
Itching - 1 (6.7%)
Rash - 2 (13.3%)
Headache - 1 (6.7%)
Inguinal and facial swelling - 1 (6.7%)

<u>Abnormal Laboratory Tests</u>

Decreased Hgb - 1
Decreased Hct - 1
Increased platelets - 2
Increased AST - 1
Increased ALT - 1

<u>Pharmacokinetics</u>

Blood samples were taken from 4 patients on at least two occasions during the course of their treatment for assay of sulbactam and ampicillin concentrations.

The pharmacokinetic data for the 4 patients are present below:

Pt. Number and Dose	Day	Peak Serum Conc (mg/L)		Serum half-life (hrs)		AUC (mg/L.hr)	
		Sulb	Amp	Sulb	Amp	Sulb	Amp
1							
0.5g Sulb+0.5g Amp	1	38.1	25.6	1.27	1.23	68.7	43.1
0.5g Sulb+0.5g Amp	5	37.4	22.8	1.70	1.58	67.0	34.2
2							
0.5g Sulb+2 g Amp	9	25.2	43.2	0.47	0.62	18.0	39.6
0.5g Sulb+2.g Amp	18	29.9	62.6	1.06	1.22	30.6	65.6
3							
0.5g Sulb+2 g Amp	2	10.4	14.6	0.86	0.88	13.0	17.8
0.5g Sulb+2.g Amp	15	19.7	37.0	0.94	0.84	18.3	39.4
4							
0.5g Sulb+2 g Amp	1	22.2	44.5	0.89	0.87	45.3	79.3
0.5g Sulb+2.g Amp	6	28.0	65.0	1.09	0.97	37.1	69.2

A sample of pus from peritonsillar abscesses was taken from 3 patients and assayed for sulbactam and ampicillin concentrations. Results are shown below:

Drug Dose	Time After Dose (hrs)	Drug Conc. in Pus (mg/L)
0.5 g Sulbactam	0.1	12.7
2 g Ampicillin	0.1	15.6
0.5 g Sulbactam	1.0	6.5
2 g Ampicillin	1.0	N.A.
0.5 g Sulbactam	4.0	1.6
2 g Ampicillin	4.0	2.6

These data show that adequate concentrations of sulbactam and ampicillin were present in pus very soon after completion of drug administration and detectable levels persisted for at least 4 hours.

2- Protocol #28-2

Title: An Open Study to Assess the Safety, Toleration, Efficacy and Pharmacokinetics of Parenteral Therapy with Sulbactam plus Ampicillin

Investigators: Prof. B. Christoforov and Prof. J. Guerre, Hospital Cochin, Paris, France

Study Design

Open, non-comparative study of multiple intramuscular doses of sulbactam and ampicillin.

Patients

Seventeen adult patients, fifteen with urinary tract infections and two with respiratory tract infections were entered into this study.

Demographic Summary

Age (years)	
Range:	32-70
Mean:	62.5

Sex	
Male:	7
Female:	10

Dose and Route of Administration

All patients were treated with sulbactam 500 mg plus ampicillin 500 mg every 8 hours by the intramuscular route.

Duration of Therapy

Fourteen patients were treated for 10 days and 3 for 11 days.

EVALUATION

EFFICACY

No. of Cases Evaluable: 14
No. of Cases Unevaluable: 3

Reasons Cases Unevaluble

No pre-treatment culture: 2
Resistant organism isolated: 1

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE
URINARY TRACT		
Cystitis (Uncomplicated)	9	9 (100%)
Cystitis (Complicated)	1	1 (100%)
Pyelonephritis (Uncomplicated)	3	3 (100%)
Pyelonephritis (Complicated)	1	1 (100%)
	14	14 (100%)

ORGANISMS	No.	BACTERIOLGIC RESPONSE ERADICATED
AMPICILLIN-SENSITIVE UNCOMPLICATED UTI		
E. Coli	5	5 (100%)
S. faecalis	1	1 (100%)
COMPLICATED UTI		
E. coli	1	1 (100%)
AMPICILLIN-RESISTANT UNCOMPLICATED UTI		
E. coli	4	4 (100%)
K. pneumoniae	1	1 (100%)
E. cloacae	1	1 (100%)
COMPLICATED UTI		
P. stuartii	1	1 (100%)

SAFETY

No. of Patients: 17
No. with Local Side Effects: 7 (41%)
No. with Systemic Side Effects: 0

LOCAL SIDE EFFECTS

Pain at intramuscular injection site: 7 (41%)

Abnormal Laboratory Tests

Decreased platelets - 2
Increased eosinophils - 1
Increased AST - 1

Pharmacokinetics
The concentrations of sulbactam and ampicillin in the serum were determined in patient at the start of treatment (1st dose), mid-treatment and at the end of treatment. Total urine collections were made whenever possible at the same times up to 8 hours after dosing.

Summary of Pharmcokinetic Data

	Peak Conc. (mg/L)		AUC (mg/L.hr)		Half-life(hr)		Time to Peak(hr)	
	Sulb	Amp	Sulb	Amp	Sulb	Amp	Sulb	Amp
Start (day 1)	15.9	15.9	50.1	48.8	2.59	2.15	0.5-2	0.5-2
Mid (day 3-7)	17.5	18.3	62.7	61.0	2.45	1.80	0.5-1	0.5-2
End (day 8-10)	17.1	16.0	59.2	56.6	2.40	1.78	0.5-2	0.5-2

Summary of Urinary Excretion

	PERCENT OF DOSE EXCRETED (0-8 hrs)	
	SULBACTAM	AMPICILLIN
Start (day 1)(n=8)	62.0	55.0
Mid (day 3-7)(n=6)	54.6	76.2
End (day 8-10)(n=6)	68.6	77.4

n= number of patients

These data show that the serum pharmacokinetic properties of both drugs are very similar with only small changes evident when start of treatment, mid-treatment and end of treatment data are compared. The only differences which are statistically significant are the mid and end of treatment half-lives of ampicillin, 1.80 hrs ($p < 0.1$) and 1.78 hrs ($p < 0.05$), relative to that at the start of treatment (2.15 hrs).

3- Protocol #34-1
Title: Open Non-Comparative Study to Assess Safety, Toleration and Efficacy of Combination Parenteral Therapy with Sulbactam and Ampicillin in Patients with Infections of the Respiratory Tract.

Investigator: Dr. A. Pines, MA, M.D. Herts and Essex Hospital, Bishops Stortford and Hertford County Hospital, Hertford, U.K.

Study Design:
Open, non-comparative study of multiple parenteral doses of a 1:1 ratio sulbactam:ampicillin.

Patients
Thirty-five adult patients with infections of the respiratory tract were entered in this study.

Demographic Summary

Age (years)
- Range: 34-80
- Mean 65.9

Sex
- Male - 26
- Female - 9

Dose and Route of Administration

All patients received sulbactam plus ampicillin in a 1:1 ratio; 19 were given 1.5 g (500 mg tid) of each, and 14 patienrs received the same dose 6-hourly (2 g + 2g daily). Two patients received one and two doses, respectively.

In 22 patients the combination was administered by the intramuscular route and in 13 by intravenous infusion.

Duration of Therapy

Duration of therapy ranged from 1 dose to 16 days with a mean duration of 7.0 days.

EVALUATION

EFFICACY

No. of Cases Evaluable: 13
No. of Cases Unevaluable: 22

Reasons Cases Unevaluable

No pre-treatment culture	- 3
No pre-treatment pathogen	- 13
Diagnosis not confirmed by X-rays	- 1
Resistant organism isolated	- 1
No post-treatment culture	- 1
Patient expired of Ca of the lungs	- 1
Patient expired of MI after only 2 doses	- 1
Patient received only one dose (hospital supply shortage)	- 1

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE	CLINICAL RESPONSE IMPROVE
LOWER RESPIRATORY			
Bronchitis	13	2(15.4%)	11(84.6%)

ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	BACTERIOLOGIC RESPONSE NOT ERADICATED
AMPICILLIN-SENSITIVE			
H. parainfluenzae	3	2 (66.7%)	1 (33.3%)
H. influenzae	5	3 (60%)	2 (40%)
E. coli	2		2 (100%)
Haemophilus sp.	1	1 (100%)	
N. catarrhalis	3	3 (100%)	
AMPICILLIN-RESISTANT			
K. pneumoniae	1	1 (100%)	
B. catarrhalis	1	1 (100%)	

One patient developed a superinfection with E. coli which required treatment with another antibiotic.

SAFETY
No. of Patients - 35
No. with Local Side Effects from I.M. Injection - 5/22 (22.7%)
No. with Local Side Effects from I.V. Injection - 0
No. with Systemic Side Effects - 1 (2.9%)

LOCAL SIDE EFFECTS
Pain at I.M. injection site - 4 (18.2%)
Sterile abscess at I.M. injection site - 1 (4.5%)

SYSTEMIC SIDE EFFECT
Diarrhea - 1 (2.9%)

Abnormal Laboratory Tests
Increased eosinophils - 1
Increased blood urea - 1
Increased alk. phosphatase - 1

4- Protocol #35-1
Title: An Open Non-Comparative Study to Assess the Efficacy and Safety of Combination Parenteral Therapy with Sulbactam and Ampicillin in Patients with Acute Infections of Skin and Soft Tissue.

Investigator: Prof. A.M. Geddes, MBChB, FRCP, East Birmingham Hospital, Birmingham, U.K.

Patients:
Twenty-five adult patients, 23 with skin and skin structure infections and one with a lower respiratory tract infection, were enrolled in this study.

Demographic Summary

Age (years)	
Range:	18-88
Mean:	42.8

Sex	
Male:	19
Female:	6

Dose and Route of Administration
All patients received sulbactam 2 g daily (500 mg qid) in a 1:2 combination with ampicillin by intravenous injection.

Duration of Therapy
Duration of therapy range from 1 to 16 days with a mean duration of 5.9 days.

...ATION

EFFICACY
No. of Cases Evaluable: 11
No. of Cases Unevaluable: 14

Reasons Cases Unevaluable
No pre-treatment pathogen - 12
Resistant organism isolated - 1
Treatment changed when organism
was found to be susceptible to penicillin - 1

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE	CLINICAL RESPONSE IMPROVE
LOWER RESPIRATORY			
Bronchitis	1		1 (100%)
SKIN & SKIN STRUCTURE			
Cellulitis	6		6 (100%)
Abscess	4	1 (25%)	3 (75%)
Total	10	1 (10%)	9 (90%)

LOWER RESPIRATORY ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
AMPICILLIN-SENSITIVE		
H. influenzae	1	1 (100%)
SKIN & SKIN STRUCTURE AMPICILLIN-SENSITIVE ORGANISMS		
S. sanguis	1	1 (100%)
S. pyogenes	2	2 (100%)
S. milleri	1	1 (100%)
S. aureus	3	3 (100%)
AMPICILLIN-RESISTANT		
S. aureus	5	5 (100%)

SAFETY
No. of Patients - 25
No. with Local Side Effects: 2 (8%)
No. with Systemic Side Effects: 2 (8%)

LOCAL SIDE EFFECTS
Thrombophlebitis - 1 (4%)
Pain at I.V. injection site - 1 (4%)

SYSTEMIC SIDE EFFECTS
Rash - 1 (4%)
Dysuria - 1 (4%)
Vaginal candidiasis - 1 (4%)

Abnormal Laboratory Tests
Increased AST - 3 cases

5- Protocol #38-1
Title: An Open Non-Comparative Study of the Efficacy and Safety of a Combination of Sulbactam plus Ampicillin in the Treatment of Serious Infections

Investigator: Dr. P. Kontomichalou, Assistant Professor of Microbiology, Alexandra Hospital, Athens, Greece

Study Design
Open, non-comparative study of multiple intravenous doses of sulbactam in combination with ampicillin (1:1 ratio) in patients with serious urinary tract infections.

Patients
Nineteen adult patients, all with urinary tract infections, were enrolled in this study.

Demographic Summary

Age (years)	
Range:	44-80
Mean:	64.5

Sex	
Male:	6
Female:	13

Dose and Route of Administration
Patients received intravenous injections of sulbactam (4 g daily; 1 g qid) in 1:1 combination with ampicillin. In one case, sulbactam 1 g 8-hourly was given with ampicillin 1 g 6-hourly for the first three days because the blood urea was elevated due to extra-renal causes. Otherwise, treatment was 6-hourly with both compounds.

Duration of Treatment
The duration of treatment ranged from 2 to 9 days with a mean duration of 6.6 days.

EVALUATION

EFFICACY
No. of Cases Evaluable: 9
No. of Cases Unevaluable: 10

Reasons Cases Unevaluable
Resistant organism isolated - 2
Treatment discontinued due to side effects - 1
No post-treatment culture - 7

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE
URINARY TRACT		
Pyelonephritis (uncomplicated)	8	8
Pyelonephritis (complicated)	1	1
Total	9	9 (100%)

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Uncomplicated UTI AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
E. coli	3	3 (100%)
P. mirabilis	2	2 (100%)
K. oxytoca	1	1 (100%)
K. pneumoniae	2	2 (100%)
COMPLICATED UTI AMPICILLIN-RESISTANT ORGANISMS		
P. mirabilis	1	1 (100%)

SAFETY
No. of Patients: 19
No. with Local Side Effects: 2 (10.5%)
No. with Systemic Side Effects: 2 (10.5%)

LOCAL SIDE EFFECTS
Pain at I.V. injection site: 2 (10.5%)

SYSTEMIC SIDE EFFECTS
Glossitis - 1 (5.3%)
Erythema - 1 (5.3%)
Itching - 1 (5.3%)

Abnormal Laboratory Tests
Increased AST - 5
Increased ALT - 2
Increased alk. phosphatase - 1
Increased bilirubin - 1

6. Protocol #42-1
Title: An Open Non-Comparative Study; A Combination of Sulbactam Plus Ampicillin in Serious Infections

Investigators: P.D. Dr. Wernicke and Professor Dr. H.G. Sonntag, Klinikum der Universitat Heidelberg, Heidelberg, Germany

Study Design:
Open, non-comparative study of the efficacy and safety of sulbactam plus ampicillin in the treatment of patients with serious infections.

Patients
Fifteen adult female patients, most of which were seriously ill with gross infections, were enrolled in this study. In 10 patients infections were associated with advanced carcinoma.

Demographic Summary

Age (years)	
Range:	21-75
Mean:	52.1

Sex
Male: 0
Female: 15

Dose and Route of Administration
Six patients received sulbactam in a 1:1 combination with ampicillin (500 mg tid) by intravenous injection. The remaining 9 patients received the combination by intravenous infusion. In these patients the dosage of sulbactam ranged from 1500 mg to 3000 mg daily (500 mg - 100 mg tid) in 1:1 combination (2 patients), 1:2 combination (6 patients) and 1:10 combination (1 patients).

Duration of Treatment
The duration of treatment ranged from 4 to 7 days with a mean duration of 5.3 days.

EVALUATION

EFFICACY
No. of Cases Evaluable: 7
No. of Cases Unevaluable: 8

Reasons Cases Unevaluble
Resistant organism isolated - 1
No susceptibility testing done - 5
Concomitant antibiotic - 1
Patient died of metastatic carcinoma during treatment - 1

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE	IMPROVE
GYNECOLOGIC			
Pelvic abscess	3		3 (100%)
Vaginal stump infection	1		1 (100%)
Tubo-ovarian abscess	1		1 (100%)
Endometritis	1	1 (100%)	
TOTAL	6	1 (16.7%)	5 (83.3%)
SKIN & SKIN STRUCTURE			
Wound infection	1		1 (100%)

GYNECOLOGIC AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
Enterococcus	1	1 (100%)	
E. coli	4	3 (75%)	1 (25%)
P. mirabilis	1	1 (100%)	
Bacteroides sp.	1	1 (100%)	

AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
E. coli	2	1 (50%)	1 (50%)
K. oxytoca	1		1 (100%)

SKIN & SKIN STRUCTURE AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
E. coli	1		1 (100%)

AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
M. morganii	1	1 (100%)	1 (100%)
Enterobacter sp.	1	1 (100%)	

Four organisms were replaced by other pathogens at the end of treatment; two patients developed reinfections after completion of treatment.

SAFETY
No. of Patients: 15
No. with Local Side Effects: 0
No. with Systemic Side Effects: 0

Deaths
One patient died of advanced metastatic carcinoma during treatment.

Abnormal Laboratory Tests
Decreased neutrophils - 1 case
Increased ALT - 1 case

7- Protocol #45-1
Title: An Open Non-Comparative Study; A Combination of Sulbactam with Ampicillin in Serious Infections

Investigator: Professor Dr. med H.M. Theopold, Klinikum Grosshadern and Institute Max von Pettenkofer, Munich, Germany

Study Design
Open, non-comparative study.

Patients
Eighteen adult patients, 7 with ENT infections, 9 with skin and skin structure infections and 2 with respiratory tract infections, were enrolled in this study.

Demographic Summary
Age (years)
Range: 28-70
Mean: 49.6

Sex
Male: 13
Female: 5

Dose and Route of Administration
Patients were treated with sulbactam 0.5 g tid in combination with ampicillin at a ratio of 1:4 in 10 patients and at a ratio of 1:10 in 8 patients, by intravenous infusion.

Duration of Treatment
The duration of treatment ranged from 5 to 11 days with a mean duration of 6.4 days.

EVALUATION

EFFICACY
No. of Cases Evaluable: 8
No. of Cases Unevaluable: 10

Reasons Cases Unevaluable
No pre-treatment pathogen - 3
No pre-treatment culture - 1
Inadequate pre-treatment culture - 4
No post-treatment culture - 1
Tonsillectomy during treatment
for tonsillar abscess - 1

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE
SKIN & SKIN STRUCTURE		
Abscess	2	2
Wound infection	2	2
Total	4	4 (100%)

UPPER RESPIRATORY	No.	CURE	IMPROVE
Epiglottic abscess	1	1	
Paryngeal abscess	1		1
Otitis media	1		1
Peritonsillar abscess	1		1
Total	4	1 (25%)	3 (75%)

SKIN & SKIN STRUCTURE

AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
Citrobacter sp.	1	1 (100%)	
P. mirabilis	1	1 (100%)	
S. epidermidis	2	1 (50%)	1 (50%)

AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
S. aureus	2	2 (100%)	
K. pneumoniae	1	1 (100%)	
M. morganii	1	1 (100%)	

UPPER RESPIRATORY

AMPICILLIN-SENSITIVE ORGANISMS	No.	ERADICATED	NOT ERADICATED
H. influenzae	1	1 (100%)	
E. coli	1		1 (100%)
S. epidermidis	1		1 (100%)

AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
K. pneumoniae	1	1 (100%)

SAFETY
There were no local or systemic adverse reactions reported in this study.

Abnormal Laboratory Tests
Increased AST - 2 cases
Increased ALT - 1 cases

8- Protocol #51-1
Title: An Open Non-Comparative Study; A Combination of Sulbactam with Ampicillin in Serious Infections

Investigator: L. Gomme, M.D., Burgerlijk Hospital, Ronse, Belgium

Study Design
Open, non-comparative study

Patients
Twenty seriously ill adult patients were enrolled in this study.

Demographic Summary
Age (years)
Range: 26-82
Mean: 70.7

Sex
Male: 12
Female: 8

Dose and Route of Administration
All patients received 3 g of sulbactam daily (1 g tid) and ampicillin 6 g daily (2 g tid) by intravenous infusion.

Duration of Treatment
The duration of treatment ranged from 4 to 13 days with a mean duration of 8.5 days.

EVALUATION

EFFICACY
No. of Cases Evaluable: 10
No. of Cases Unevaluable: 10

Reasons Cases Unevaluable
No pre-treatment pathogen - 4
No post-treatment culture - 2
Concomitant antibiotic - 1
Diagnosis not confirmed - 2
Died during treatment of cardiovascular collapse - 1

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE	IMPROVE
BACTEREMIA*	5	4 (80%)	1 (20%)
LOWER RESPIRATORY			
Pneumonia	1	1	
Bronchitis	1		1
TOTAL	2	1 (50%)	1 (50%)
UTI (UNCOMPLICATED)	3	1 (33.3%)	2 (66.7%)

*Bacteremia is defined as only one positive blood culture before treatment.

BACTEREMIA AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
Enterococcus	1	1 (100%)
E. coli	2	2 (100%)
AMPICILLIN-RESISTANT ORGANISMS		
E. coli	1	1 (100%)
Y. enterocolitica	1	1 (10^%)
LOWER RESPIRATORY AMPICILLIN-SENSITIVE ORGANISMS		
S. pneumoniae	2	2 (100%)
H. influenzae	1	1 (100%)
AMPICILLIN-RESISTANT ORGANISMS		
K. oxytoca	1	1 (100%)
UTI (UNCOMPLICATED) AMPICILLIN-SENSITIVE ORGANISMS		
E. coli	1	1 (100%)
AMPICILLIN-RESISTANT ORGANISMS		
P. mirabilis	1	1 (100%)
K. oxytoca	1	1 (100%)

SAFETY

There were no local or systemic side effects reported in this study.

Deaths

There were 3 deaths reported in this study. None was considered by in the investigator to be drug related.

ABNORMAL LABORATORY TESTS

Decreased Hgb	- 3 cases
Decreased Hct	- 1 case
Increased Eosinophils	- 1 case
Increased alk. phosphatase	- 2 cases

9- Protocol #52-1
Title: An Open Non-Comparative Study to Assess the Efficacy and Safety of a Combination of Sulbactam and Ampicillin in the Treatment of Serious Infections.

Investigator: Dr. S. Mehtar, MBBS, MRC Path, North Middlesex Hospital, London, U.K.

Study Design
Open, non-comparative study of multiple parenteral doses of sulbactam plus ampicillin (in 1:1 combination) in patients with serious infections.

Patients
Thirty-one adult patients were enrolled in this study.

Demographic Summary
Age (years)
Range: 17-84
Mean: 55.7

Sex
Male: 21
Female: 10

Dose and Route of Administration
The daily dose of sulbactam was 500 mg qid in 1:1 combination with ampicillin. One patient received 1 g qid of sulbactam in 1:1 combination with ampicillin for the last 3 days of treatment, then received the lower dose.
Thirteen patients received the drugs by intravenous injection, one by intravenous infusion, thirteen by intramuscular injection and four by both intravenous and intramuscular administration.

Duration of Treatment
The duration of treatment ranged from 2 to 16 days with a mean duration of 5.8 days.

EVALUATION

EFFICACY
No. of Cases Evaluable: 17
No. of Cases Unevaluable: 14

Patients
Thirty-one adult patients were enrolled in this study.

Reasons Cases Unevaluable
No pre-treatment pathogen - 4
Diagnosis of appendicitis but without peritonitis - 4
No post-treatment culture - 3
Concomitant antibiotic - 1
Patient died during treatment - 2 (One of a respiratory arrest and one of cardiac failure)

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE	CLINICAL RESPONSE IMPROVE
BACTEREMIA	3	2 (66.7%)	1 (33.3%)
LOWER RESPIRATORY			
Bronchitis	1	1	
Pneumonia	2	1	1
Bronchopneumonia	5	2	3
Empyema	1		1
TOTAL	9	4 (44.4%)	5 (55.6%)

INTRA-ABDOMINAL	No.	CLINICAL RESPONSE CURE	CLINICAL RESPONSE IMPROVE
Peritonitis	1	1	
Abscess	2	1	1
Cholecystitis	1	1	
TOTAL	4	3 (75%)	1 (25%)
SKIN & SKIN STRUCTURE			
Wound infection	1	1 (100%)	

BACTEREMIA AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	BACTERIOLOGIC RESPONSE NOT ERADICATED
S. aureus	1	1 (100%)	
E. coli	1	1 (100%)	
Klebsiella sp.	1	1 (100%)	
LOWER RESPIRATORY AMPICILLIN-RESISTANT ORGANISMS			
B. catarrhalis	3	3 (100%)	
S. aureus	2	2 (100%)	
H. influenzae	3	3 (100%)	
H. parainfluenzae	2	2 (100%)	

table continued

INTRA-ABDOMINAL AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
E. coli	1	1 (100%)	
Streptococcus sp.	1	1 (100%)	
AMPICILLIN-RESISTANT ORGANISMS			
S. faecalis	1	1 (100%)	
E. coli	1		1 (100%)
E. aerogenes	1	1 (100%)	
B. fragilis	2	2 (100%)	
B. melaninogenicus	1	1 (100%)	
SKIN & SKIN STRUCTURE AMPICILLIN-SENSITIVE ORGANISMS			
Streptococcus sp.	1	1 (100%)	
P. mirabilis	1	1 (100%)	
AMPICILLIN-RESISTANT ORGANISMS			
B. fragilis	1	1 (100%)	

SAFETY
No. of Patients: 31
No. with Local Side Effects: 10 (32.2%)
No. with Systemic Side Effects: 1 (3.2%)

LOCAL SIDE EFFECTS
Pain at I.M. injection site: 6/17 (35.3%)
Pain at I.V. injection site: 3/18 (16.7%)
Thrombophlebitis: 1/18 (5.6%)

SYSTEMIC SIDE EFFECT
Diarrhea - 1 (3.2%)

Deaths
There were 2 deaths reported in this study. None was considered by the investigator to be drug related.

ABNORMAL LABORATORY TESTS
Decreased Hgb - 1
Decreased Hct - 1
Increased eosinophils - 1
Increased platelets - 5
Increased SGOT - 5
Increased alk. phosphatase - 1

10- Protocol #52-2
Title: An Open Non-Comparative Study to Assess the Safety, Toleration and Safety of Sulbactam Plus Ampicillin in Serious Infections

Investigator: Dr. S. Mehtar, MMDS, MRCPath, North Middlesex Hospital, London, U.K.

Study Design

Open, non-comparative study of the efficacy and safety of multiple intravenous doses of sulbactam in 1:2 combination with ampicillin.

Patients

Twenty-three patients (19 with acute intra-abdominal infections and 4 with respiratory tract infections) were enrolled in this study.

Demographic Summary

Age (years)

Range: 7-10: 3 patients
Mean: 13-86: 20 patients

Sex

Male: 14
Female: 9

Dose and Route of Administration

All patients received 6-hourly injections of sulbactam in 1:2 combination with ampicillin. Two children, aged 7 and 8 years, were given 1 g of sulbactam daily (250 mg qid); the remainder patients received 2 g sulbactam daily (500 mg qid) all in 1:2 combination with ampicillin. Eighteen patients received the drugs by I.V. injections, 3 by I.M. injections and 2 by both I.V. and I.M. injections.

Duration of Treatment

The duration of teatment ranged from 3-10 days with a mean duration of 5.4 days.

EVALUATION

EFFICACY

No. of Cases Evaluable: 12
No. of Cases Unevaluable: 11 (8 adults, 3 children)

Reason Cases Unevaluable

No pre-treatment pathogen - 5
Concomitant antibiotic - 1
Diagnosis of appendicitis but without peritonitis - 5

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE	IMPROVE	FAIL
LOWER RESPIRATORY				
Bronchitis	2		1	1
Bronchopneumonia	2		2	
TOTAL	4		3 (75%)	1 (25%)
INTRA-ABDOMINAL				
Peritonitis	8	4 (50%)	2 (25%)	2 (25%)

LOWER RESPIRATORY AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
B. catarrhalis	1	1 (100%)	
S. aureus	2	2 (100%)	
H. influenzae	2	2 (100%)	
H. parainfluenzae	1	1 (100%)	
E. coli	1	1 (100%)	
Klebsiella sp.	1	1 (100%)	
INTRA-ABDOMINAL AMPICILLIN-SENSITIVE ORGANISMS			
Streptococcus sp.	4	4 (100%)	
P. mirabilis	1	1 (100%)	
AMPICILLIN-RESISTANT ORGANISMS			
E. coli	8	5 (62.5%)	3 (37.5%)
M. morganii	1	1 (100%)	
Klebsiella sp.	1		1 (100%)
K. oxytoca	1	1 (100%)	
B. fragilis	4	4 (100%)	
B. melaninogenicus	1	1 (100%)	

One patient with a lower respiratory infection and an underlying adenocarcinoma of the lung developed a re-infection at the completion of treatment and was considered a clinical failure.

SAFETY
No. of Patients: 23
No. with Local Side Effects: 7 (30.4%)
No. with Systemic Side Effects: 1 (4.3%)

LOCAL SIDE EFFECTS
Pain at I.M. injection site: 2/5 (40%)
Pain at I.V. injection site: 4/20 (20%)
Thrombophlebitis: 1/20 (5%)

SYSTEMIC SIDE EFFECTS
Nausea - 1 (4.3%)
Vomiting - 1 (4.3%)
Diarrhea - 1 (4.3%)

Deaths
Three patients died during the study. A 72 year old man died after 10 days of treatment as a result of a small bowel fistula. Two others died after treatment had ceased; one from a cerebrovascular accident and the other from a bleeding ulcer.

ABNORMAL LABORATORY TESTS
Increased AST -3
Increased bilirubin - 2
Increased blood urea - 1

11- Protocol # 54-1

Title: An Open Non-Comparative Study to Assess the Efficacy, Safety and Toleration of Sulbactam Plus Ampicillin in Patients with Serious Infections

Investigator: Dr. G. Siska, M.D., Unite de Pharmacologie Clinique, Montigny le Tilleur, Belgium

Study Design:
Open, non-comparative study of the efficacy and safety of multiple intravenous doses of sulbactam in a 1:1 combination with ampicillin.

Patients
Sixteen adult patients (2 with skin and skin structure infections and 14 with undefined urinary tract infections) were enrolled in this study.

Demographic Summary

Age (years)
Range : 63-96
Mean: 77.9

Sex
Male: 5
Female: 11

Dose and Route of Administration
All patients received sulbactam and ampicillin in a 1:1 ratio. Eleven patients received 2 g of each compound daily as 500 mg qid, 4 patients received 1.5 g of each compound as 500 mg tid, and one patient received 4 g of each compound as 1 g qid.
In 14 patients the dose was administered by I.M. injection throughout; one received I.V. bolus injections, and one received I.V. bolus injections for 7 days followed by 2 days of I.M. injections.

Duration of Treatment
The duration of treatment ranged from 7-12 days with a mean duration of 8.8 days.

EVALUATION

EFFICACY
No. of Cases Evaluable: 13
No. of Cases Unevaluable: 3

Reasons Cases Unevaluable
Resistant organism isolated: 1
No post-treatment culture: 2

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE	IMPROVE	FAIL
UTI (Uncomplicated)	7		6 (85.7%)	1 (14.3%)
UTI (Complicated)	4		4 (100%)	

table continued

SKIN & SKIN STRUCTURE	No.	CLINICAL RESPONSE CURE	IMPROVE	FAIL
Ulcer	1	1 (100%)		
Abscess	1		1 (100%)	

UTI (Uncomplicated) AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
E. coli	7	4 (57%)	3 (43%)

UTI (Complicated) AMPICILLIN-RESISTANT ORGANISMS	No.	ERADICATED	NOT ERADICATED
E. coli	4	4 (100%)	

SKIN & SKIN STRUCTURE AMPICILLIN-RESISTANT ORGANISMS	No.	ERADICATED	NOT ERADICATED
S. aureus	2	2 (100%)	

One patient with a complicated urinary tract infection had a relapse one week following completion of therapy.

SAFETY
No. of Patients: 16
No. with Local Side Effects: 12 (75%)
No. with Systemic Side Effects: 1 (6.25%)

LOCAL SIDE EFFECT
Pain at I.M. injection site - 12/15 (80%)

SYSTEMIC SIDE EFFECTS
Diarrhea - 1 (6.25)
Rash - 1 (6.25)

Deaths
Two patients died during the follow-up period from causes unrelated to treatment.

ABNORMAL LABORATORY TESTS
Increased eosinophils - 1 case

12- Protocol #65-1
Title: An Open Non-Comparative Study of Sulbactam Plus Ampicillin in the Treatment of Serious Infections

Investigator: Professor J. Dalayeun, Hospital Suisse, Issy Les Moulineaux, France

Study Design
Open, non-comparative study to assess the efficacy, toleration and safety of sulbactam plus ampicillin in the treatment of infections caused by pathogens potentially resistant to ampicillin.

Patients
Only one patient with an undefined urinary tract infection took part in this study.

Age: 67 years
Sex: Female

Dose and Route of Administration
The patient was treated with sulbactam 2 g daily (500 mg qid) plus ampicillin 4 g daily (1 g qid) by intravenous infusion.
The duration of treatment was 10 days.

EVALUATION

EFFICACY
No. of Cases Evaluable: 1

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE
UTI (Uncomplicated)	1	1 (100%)

AMPICILLIN-SENSITIVE ORGANISM	No.	BACTERIOLOGIC RESPONSE ERADICATED
E. coli	1	1 (100%)

SAFETY
There were no treatment related local or systemic side effects, nor were there any drug-related laboratory abnormalities.

13- Protocol #37-1
Title: An Open Non-Comparative Study of Sulbactam Plus Ampicillin in the Treatment of Serious Infections

Investigator: Professor M. Micoud, Centre Hospitalier Regional, Clinique de Maladies Infectieuses, La Tronche, France

Study Design:
Open, non-comparative study to assess the efficacy, toleration and safety of sulbactam plus ampicillin in the treatment of infections caused by pathogens potentially resistant to ampicillin.

Patients
Only one patient with pyelonephritis took part in this study.

Age: 40
Sex: Female

Dose and Route of Administration
The patient was treated with sulbactam 2 g (500 mg qid) plus ampicillin 4 g (1 g qid) by intravenous injection for only one day.
Treatment was discontinued when the patient was found to be infected with an ampicillin sensitive pathogen. Therefore, this case is considered unevaluable for both efficacy and safety analyses.

14- Protocol #67-1

Title: An Open Non-Comparative Study to Assess the Efficacy and Safety of Sulbactam Plus Ampicillin in Severe Infections of the Respiratory Tract

Investigator: Dr. C. Gillard, Pneumology Department, Civil Hospital, Jumet, Belgium

Study Design:
An open, non-comparative study to assess the efficacy and safety of multiple parenteral doses of sulbactam plus ampicillin in severe respiratory tract infections.

Patients
Eleven adult patients with severe respiratory tract infections took part in this study.

Demographic Summary
Age (years)
Range: 39-78
Mean: 62.7

Sex
Male: 7
Female: 4

Dose and Route of Administration
Six patients received ampicillin in combination with sulbactam in a 1:1 ratio, and five received ampicillin in a 1:2 ratio. Eight patients started treatment with 4 grams of sulbactam daily (1 g qid) administered by intravenous bolus injection.
One patient started on 1 g 4-hourly of sulbactam by intravenous infusion, and two others started treatment with 500 mg tid or qid, respectively, by intramuscular injection.
In 5 patients the dosage was reduced to 1.5-2.0 g daily and given by intramuscular injection after 3-5 days.

Duration of Treatment
The duration of treatment ranged from 2-10 days with a mean duration of 7.1 days.

EVALUATION

EFFICACY
No. of Cases Evaluable: 3
No. of Cases Unevaluable: 8

Reasons Cases Unevaluable
No pre-treatment pathogen - 5
Resistant organism isolated - 2
Another antibiotic given by error
before post-treatment cultures taken - 1

RESULTS

INFECTION LOWER RESPIRATORY	No.	CLINICAL RESPONSE CURE	IMPROVE
Bronchitis	1	1 (100%)	
Pneumonia	2	1 (50%)	1 (50%)

LOWER RESPIRATORY AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
S. pneumoniae	2	2 (100%)

AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
S. aureus	1	1 (100%)

SAFETY
No. of Patients: 11
No. with Local Side Effects: 5 (45.5%)
No. with Systemic Side Effects: 2 (18.2%)

LOCAL SIDE EFFECTS
Pain at I.M. injection site: 2/7 (28.6%)
Pain at I.V. injection site: 2/9 (22.2%)
Thrombophlebitis: 1/9 (11.1%)

SYSTEMIC SIDE EFFECTS
Nausea - 1 (9.1%)
Vomiting - 1 (9/1%)

Deaths
One patient died 6 days after treatment was discontinued. Death was not considered to be drug-related.

ABNORMAL LABORATORY TESTS
Increased eosinophils - 1 case

15- Protocol #70-1
Title: An Open Non-Comparative Study of Sulbactam Plus Ampicillin in the Treatment of Serious Infections

Investigator: Dr. Hannu Kyronseppa, Aurora, Finland

Study Design
Open, non-comparative study to assess the efficacy and safety of sulbactam plus ampicillin after multiple intravenous dosing.

Patients
Only two patients were enrolled in this study.

Demographic Summary
Age (years)
Range: 32-46
Mean: 39

Sex
Female - 2

Dose and Route of Administration
Patients were treated with sulbactam 2 g daily (500 qid) plus ampicillin 4 g daily (1 g qid) by intravenous infusion (1 patient) or intravenous injection (1 patient). After 3 and 4 days, both patients were switched to intramuscular administration.

Duration of Treatment
The duration of treatment was 10 and 14 days, respectively.

EVALUATION

EFFICACY
No. of Cases Evaluable: 1
No. of Cases Unevaluable: 1

Reason Case Unevaluable
No susceptibility testing done - 1

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE
Bacteremia	1	1 (100%)

AMPICILLIN-SENSITIVE ORGANISM	No.	BACTERIOLOGIC RESPONSE ERADICATED
E. coli	1	1 (100%)

SAFETY
No. of Cases: 2
No. with Local Side Effects: 1 (50%)
No. with Systemic Side Effects: 0

LOCAL SIDE EFFECT
Thrombophlebitis: 1 (50%)

ABNORMAL LABORATORY TESTS
Increased AST - 1
Increased ALT - 1

16- Protocol #72-1
Title: An Open Non-Comparative Study Using a Combination of Sulbactam Plus Ampicillin in Serious but not Life Threatening Infections in Pediatric Patients

Investigator: Dr. V. Syriopoulou, Aghia Sophia Children's Hospital, Athens, Greece

Study Design:
An open, non-comparative study of multiple parenteral doses of a 1:2 ratio of sulbactam : ampicillin in pediatric patients with infections caused by pathogens potentially resistant to ampicillin.

Patients
Fourteen children, 4 with acute lymphadenitis and 10 with acute urinary tract infections, took part in this study.

Demographic Summary
Age (years)

< 1 year (9 months)	- 1 patient
1 - 2 years	- 8 patients
3 - 4 years	- 3 patients
7 -10 years	- 2 patients
Mean Age	2.9 years

Sex

Male	- 4
Female	- 10

Dose and Route of Administration
The duration of treatment ranged from 4-11 days with a mean duration of 9.4 days.

EVALUATION

EFFICACY
No. of Cases Evaluable - 13
No. of Cases Unevaluable - 1

Reason Case Unevaluable
Patient continued on oral prophylactic antibiotic before post-treatment culture was taken - 1

RESULTS

INFECTION		CLINICAL RESPONSE	
SKIN & SKIN STRUCTURE	No.	CURE	FAIL
Lymphadenitis	4	4 (100%)	
UTI (Uncomplicated)	5	5 (100%)	
UTI (Complicated)	4	3 (75%)	1 (25%)

SKIN & SKIN STRUCTURE AMPICLLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
S. aureus	4	4 (100%)

UTI (Uncomplicated) AMPICILLIN-RESISTANT ORGANISM	No.	ERADICATED
E. coli	5	5 (100%)

UTI (Complicated) AMPICILLIN-RESISTANT ORGANISM	No.	ERADICATED	NOT ERADICATED
E. coli	4	3 (75%)	1 (25%)

One patient with a urinary tract infection had a relapse 12 days after discontinuation of therapy.

SAFETY

No systemic or local side effects were recorded for any of the 14 patients.

ABNORMAL LABORATORY TESTS

Decreased neutrophils - 1
Increased eosinophils - 1
Increased AST - 1
Increased ALT - 1

17- Protocol #73-1

Title: An Open, Non-Comparative Study to Assess the Efficacy and Safety of Sulbactam Plus Ampicillin in the Treatment of Gynecologic Infections

Investigator: Dr. H. Giamarellou, King Paul Hospital, Athens, Greece

Study Design

An open, non-comparative study of the efficacy and safety of multiple parenteral dosing of sulbactam plus ampicillin in gynecologic infections caused by pathogens potentially resistant to ampicillin.

Patients

Fifteen female patients, 12 with gynecologic infections and 3 with wound infections secondary to gynecologic surgery, were enrolled in this study.

Demographic Summary

Age (years)

Range - 19-52
Mean - 38.1

Sex

Female - 15

Dose and Route of Administration

Ten patients received sulbactam 4 g daily (1 g qid) in a 1:1 combination with ampcillin, and 5 patients received sulbactam 2 g daily (500 mg qid) in a 1:2 combination with ampicillin.

Thirteen patients initially were dosed intravenously and then were switched to intramuscular injections. Two patients were dosed by the intravenous route only.

Duration of Treatment

The overall treatment duration ranged from 5 to 8 days with a mean duration of 6.6 days.

EVALUATION

EFFICACY

No. of Cases Evaluable - 11
No. of Cases Unevaluable - 4

Reasons Cases Unevaluable

No susceptibility testing done	- 2
Concomitant antibiotic given	- 1
Patient continued on oral antibiotic before post-treatment culture taken	- 1

RESULTS

INFECTION GYNECOLOGIC	No.	CLINICAL RESPONSE CURE	CLINICAL RESPONSE IMPROVE
Vaginal cuff abscess	7	7 (100%)	
PID	1		1 (100%)
Endometritis	1	1 (100%)	
TOTAL	9	8 (88.9%)	1 (11.1%)

SKIN & SKIN STRUCTURE	No.	CURE
Wound infection	2	2 (100%)

GYNECOLOGIC AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
E. coli	4	4 (100%)
Enterococcus	1	1 (100%)

AMPICILLIN-RESISTANT ORGANISMS	No.	ERADICATED
E. coli	4	4 (100%)
K. oxytoca	1	1 (100%)
Bacteroides spp.	1	1 (100%)
B. fragilis	1	1 (100%)
Peptococcus spp.	1	1 (100%)

SKIN & SKIN STRUCTURE AMPICILLIN-RESISTANT ORGANISMS	No.	ERADICATED
S. epidermidis	1	1 (100%)
B. melaninogenicus	1	1 (100%)

One patient with pelvic inflammatory disease developed a superinfection with a K. pneumoniae strain resistant to the sulbactam/ampicillin combination.

SAFETY

No. of Patients - 15
No. with Systemic Side Effects - 0
No. with Local Side Effects: None of the patients complained spontaneously about any local side effects; however, upon questioning 12 patients indicated that they had experienced some pain, 9 with the intravenous injections and 3 with the intramuscular injections.

ABNORMAL LABORATORY TESTS
Increased AST - 1
Increased ALT - 1

18- Protocol #74-1

Title: An Open, Non-Comparative Study to Assess the Efficacy, Safety and Toleration of Sulbactam Plus Ampicillin in the Treatment of Patients with Infections Caused by Beta-Lactamase-Producing Bacteria

Investigator: Professor G. Burghard, M.D., Hospital Saint Francois, Strasbourg, France

Study Design:
Open, non-comparative study of multiple parenteral doses of sulbactam in combination with ampicillin in a 1:1 ratio.

Patients
Nineteen adult patients with acute bronchitis superimposed on either chronic obstructive pulmonary disease or chronic bronchitis were entered in this study.

Demographic Summary
Age (years)
Range - 43-81
Mean - 64.9

Sex
Male - 14
Female - 5

Dose and Route of Administration
All patients were treated with sulbactam and ampicillin in a 1:1 combination by intravenous infusion.

Five patients received 1.5 g (500 mg tid) of each compound daily; one received 3.0 g (1.0 g tid) daily, and 13 received 2.0 g (1.0 g bid) daily.

Duration of Treatment
The duration of treatment ranged from 2 to 10 days with a mean duration of 7.9 days.

EVALUATION
No. of Cases Evaluable - 6
No. of Cases Unevaluable - 13

Reasons Cases Unevaluable
No pre-treatment pathogen - 1
Resistant organisms isolated - 7
No susceptibility testing done - 1
Patient left hospital against medical advice after 2 days of treatment - 1
Treatment continued with oral antibiotics before cultures taken - 3

RESULTS

INFECTION LOWER RESPIRATORY	No.	CLINICAL RESPONSE IMPROVE
Bronchitis	6	6 (100%)

AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
Haemophilus spp.	1	1 (100%)	
H. influenzae	1		1 (100%)
H. parainfluenzae	3		3 (100%)

AMPICILLIN-RESISTANT ORGANISMS	No.	ERADICATED	NOT ERADICATED
S. aureus	2	1 (50%)	1 (50%)
K. pneumoniae	1		1 (100%)

SAFETY

SIDE EFFECTS
No systemic or local side effects were reported for any patient.

ABNORMAL LABORATORY TESTS	
Decreased Hgb	- 1
Decreased Hct	- 1
Decreased RBCs	- 1
Decreased WBCs	- 1
Increased eosinophils	- 2
Increased AST	- 2
Increased ALT	- 2
Increased alk. phosphatase	- 2
Increased blood urea	- 1

19- Protocol #76-1
Title: An Open, Non-Comparative Study of Sulbactam Plus Ampicillin in Patients with Serious Infections.

Investigator: Professor Andre Nenna, Hospital Raymond Poincare, Garches, France

Study Design
Open, non-comparative study of multiple parenteral doses of sulbactam in a 1:2 combination with ampicillin

Patients
Six adult patients, 3 with bacteremia and 3 with urinary tract infections were enrolled in this study.

Demographic Summary

Age (years)
Range: 31-74
Mean: 56.7

Sex
Male: 4
Female: 2

Dose and Route of Administration

All patients were treated with sulbactam and ampicillin in a 1:2 combination.
One patient received 1.5/3.0 g (500/1000 q 8 hours) daily, 3 patients received 2.0/4.2 g (500/1000 q 6 hours) daily, and one patient received 3.0/6.0 g (500/1000 q 4 hours) daily.
Two patients received tratment by I.V. infusion; one of these was changed to I.V. injections after 4 days.
Four patients received treatment by I.V. injections

Duration of Treatment

The duration of treatment ranged from 1 to 28 days, except for one patient who received only a single injection. The mean duration of treatment was 6.7 days.

EVALUATION

EFFICACY
No. of Cases Evaluable: 2
No. of Cases Unevaluable: 4

Reasons Cases Unevaluable
Resistant organism isolated - 1
No urine colony count - 1
Treatment stopped on day 1 due to poor condition of veins - 2

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE
BACTEREMIA	1	1 (100%)
UTI (Complicated)	1	1 (100%)

BACTEREMIA

AMPICILLIN-RESISTANT ORGANISM	No.	BACTERIOLOGIC RESPONSE ERADICATED
S. aureus	1	1 (100%)

UTI (Complicated)

AMPICILLIN-RESISTANT ORGANISM	No.	ERADICATED
P. mirabilis	1	1 (100%)

SAFETY
No. of Patients with Local Side Effects: 2 (33.3%)
No. of Patients with Systemic Side Effects: 0

LOCAL SIDE EFFECTS
Pain at I.V. injection site: 2 (33.3%)

ABNORMAL LABORATORY TESTS
No drug related abnormal laboratory values were reported.

20- Protocol #77-1

Title: An Open Non-Comparative Study to Assess the Pharmacokinetics, Efficacy and Safety of a Combination of Sulbactam with Ampicillin in the Treatment of Acute Exacerbations of Chronic Bronchitis

Investigators
Dr. F. Maesen and Dr. B. Davies, De Wever Ziekenhuis, Heerlen, The Netherlands

Study Design
Open, non-comparative study designed to assess the pharmacokinetics efficacy and safety of sulbactam in combination with ampicillin in patients with acute exacerbations of chronic bronchitis caused by pathogens potentially resistant to ampicillin.

Patients
Twenty adult patients with acute exacerbations of chronic bronchitis were entered in this study.
Underlying lung diseases included emphysema, asthma, bronchiectasis and silica pneumoconiosis.

Demographic Summary
Age (years)
Range: 26-78
Mean: 64.4

Sex
Male: 14
Female: 6

Dose and Route of Administration
All patients received sulbactam 1.0 g daily (0.5 g bid) in a 1:2 combination with ampicillin dissolved in 0.5 ml 2% lignocaine made up to a total volume of 4 ml and administered by intramuscular injection in the gluteal region.

Duration of Treatment
The duration of treatment ranged from 9 to 11 days (mean 9.9 days), except in one patient with metastatic carcinoma of the liver who was withdrawn from the study after the third day of treatment because of his pre-existing abnormal liver function.

EVALUATION

EFFICACY
No. of Cases Evaluable: 18
No. of Cases Unevaluable: 2

Reasons Cases Unevaluable
No pre-treatment pathogen - 1
Patient withdrawn after three days of treatment - 1
RESULTS

INFECTION LOWER RESPIRATORY	No.	CLINICAL RESPONSE CURE	IMPROVE	FAIL
Bronchitis	18	9 (45%)	7 (35%)	2 (10%)

AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
S. pneumoniae	5	5 (100%)
H. influenzae	5	5 (100%)
B. catarrhalis	3	3 (100%)

AMPICILLIN-RESISTANT ORGANISMS	No.	ERADICATED
S. aureus	1	1 (100%)
B. catarrhalis	7	7 (100%)

In two patients with ampicillin-resistant B. catarrhalis, the infection relapsed one week after discontinuation of treatment.
Four patients developed superinfections with resistant organisms (P. aeruginosa (3), K. pneumoniae (1).

Pharmacokinetics
Sulbactam and ampicillin levels were monitored in the serum and sputum of all patients for up to 7 hours after administration of the first dose. Ten patients received 0.5 g sulbactam plus 1.0 g ampicillin (low dose), and ten patients received 1.0 g sulbactam plus 2.0 g ampicillin (high dose) by intramuscular injection.

Summary of Mean Serum and Sputum Pharmacokinetic Parameters

Serum Pharmacokinetics

Drug	Peak Concentration (mg/L ± S.D.)	AUC (0-7 hrs) (mg/L.hr ± S.D)	T1/2 (hr± S.D.)	Time to Peak (hr)
Sulbactam (0.5 g)	13.3 ± 1.8	38.6 ± 3.5	2.8 ± 0.3	0.5 - 2
Ampicillin (1.0 g)	16.5 ± 1.9	53.0 ± 4.1	2.9 ± 0.7	0.5 - 3
Sulbactam (1.0 g)	23.5 ± 2.5	70.3 ± 8.2	2.2 ± 0.3	0.5 - 2
Ampicillin (2.0 g)	20.6 ± 2.5	73.1 ± 4.8	3.3 ± 1.4	0.5 - 2

Sputum Pharmacokinetics

Drug	Peak Concentration (mg/L ± S.D.)	AUC (0-7 hrs) (mg/L.hr ± S.D)	Time to Peak (hr)
Sulbactam (0.5 g)	1.14 ± 0.13	5.30 ± 0.78	3 - 5
Ampicillin (1.0 g)	1.50 ± 0.23	6.87 ± 1.21	3 - 5
Sulbactam (1.0 g)	2.32 ± 0.53	8.70 ± 1.58	1 - 5
Ampicillin (2.0 g)	1.44 ± 0.21	6.77 ± 0.94	1 - 5

Mean peak serum concentrations of sulbactam and ampicillin occurred about 1 hour after dosing in both low and high dose groups of patients. Peak sputum concentrations of both drugs were detected 2 to 3 hours later and were about one-tenth of peak serum concentrations.

SAFETY

There were no local or systemic side effects reported in this study.

Death

A 78 year old patient died 3 days after being withdrawn from treatment. The death was due to stomach cancer and liver metastases.

ABNORMAL LABORATORY TESTS

Decreased Hgb	- 1
Decreased Hct	- 1
Increased eosinophils	- 1
Increased AST	- 3
Increased ALT	- 2
Increased blood urea	- 1
Increased creatinine	- 2

21- Protocol #80-1

Title: An Open, Non-Comparative Study to Assess the Efficacy and Safety of Sulbactam Plus Ampicillin in the Treatment of Urinary Tract Infections

Investigator: Dr. J. Reynaert, St. Jozefklinick, Kortenberg, Belgium

Study Design

Open, non-comparative study designed to determine the efficacy and safety of sulbactam in combination with ampicillin in the treatment of urinary tract infections caused by pathogens potentially resistant to ampicillin.

Patients

Ten female patients with cystitis and underlying mental disorders were enrolled in this study.

Demographic Summary

Age (years)

Range: 44-76
Mean: 68.8

Sex

Female: 10

Dose and Route of Administration

All patients received sulbactam (1.5 g daily; 500 tid) and ampicillin (3.0 g daily; 1.0 g tid) by intramuscular injection.

Duration of Treatment

All patients were treated for a total of 5 days.

EVALUATION

No. of Cases Evaluable: 2
No. of Cases Unevaluable: 8

Reasons Cases Unevaluable
Resistant organism isolated - 1
Urine cultures obtained more than
one week before treatment - 7

RESULTS

INFECTION		CLINICAL RESPONSE
UTI (Uncomplicated)	No.	IMPROVE
Cystitis	2	2 (100%)

AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
E. coli	2	2 (100%)
P. maltophilia	1	1 (100%)

SAFETY
There were no treatment-related side effects reported for any of the patients.

ABNORMAL LABORATORY TESTS
Increased eosinophils - 1

22- Protocol #83-1
Title: An Open, Non-Comparative Study to Assess the Efficacy and Safety of Sulbactam Plus Ampicillin in Serious Infections

Investigator: Dr. R. G. Finch, M.B., ChB, MRCP, MRCPath, City Hospital, Nottingham, U.K.

Study Design
An open, non-comparative study designed to determine the efficacy and safety of sulbactam in combination with ampicillin in the treatment of infections caused by pathogens potentially resistant to ampicillin.

Patients
Tweleve adult patients were enrolled in this study.

Demographic Summary
Age (years)
Range: 32-82
Mean: 63.8

Sex
Male: 7
Female: 5

Dose and Route of Administration
All patients received sulbactam and ampicillin in a 1:2 ratio, intravenously.
Seven patients received 1.0/2.0g (250/500 qid), four patients received 2.0/4.0 g (500/1000 qid), and one patient received 2.0/4.0 g daily for 5 days, and then the dose was increased to 4.0/8.0 q daily for 5 more days.

Duration of Treatment
The duration of treatment ranged from 1 dose to 10 days with a mean duration of 5 days.

EVALUATION
No. of Cases Evaluable: 0
No. of Cases Unevaluable: 12

Reasons Cases Unevaluable
No pre-treatment pathogen - 8
No post-treatment culture - 3
Patient withdrawn after receiving one dose when he was found to have insulin-dependent diabetes - 1

SAFETY
No. of Patients: 12
No. with Local Side Effects: 3 (25%)
No. with Systemic Side Effects: 1 (8.3%)

LOCAL SIDE EFFECTS
Pain at I.V. injection site: 1 (8.3%)
Thrombophlebitis: 2 (16.7%)

SYSTEMIC SIDE EFFECTS
Diarrhea -1 (8.3%)

ABNORMAL LABORATORY TESTS

Decreased Hgb	- 1
Decreased Hct	- 2
Decreased RBCs	- 1
Increased platelets	- 2
Increased ALT	- 1
Increased alk. phosphatase	- 1

23- Protocol #85-1
Title: An Open, Non-Comparative Study to Assess the Efficacy and Safety of Sulbactam Plus Ampicillin in the Treatment of Pneumonia

Investigator: Primarius Dr. O. Wieser, Landeskrankenhaus Karntem, Klagenfurt, Austria

Study Design:
An open, non-comparative study to assess the efficacy and safety of multiple doses of a 1:2 combination of sulbactam and ampicillin in the treatment of pneumonia caused by pathogens potenti.lly resistant to ammpicillin.

Patients
Fifteen adult patients with documented pneumonia or bronchopneumonia were enrolled in this study.

Demographic Summary

Age (years)
Range: 40-82
Mean: 60.1

Sex
Male: 5
Female: 10

Dose and Route of Administration
All patients received sulbactam 3 g daily (1.0 g tid) plus ampicillin 6.0 g daily (2.0 g tid) by intravenous infusion.

Duration of Treatment
The duration of treatment ranged from 8 to 12 days with a mean duration of 10.3 days.

EVALUATION

EFFICACY
No. of Cases Evaluable: 7
No. of Cases Unevaluable: 8

Reasons Cases Unevaluable

No pre-treatment pathogen	- 3
Resistant organism isolated	- 1
Concomitant antibiotic	- 1
Sputum culture taken more than one week before treatment	- 2
No post-treatment culture	- 1

RESULTS

INFECTION LOWER RESPIRATORY	No.	CLINICAL RESPONSE CURE	IMPROVE
Pneumonia	7	4 (57.1%)	3 (42.9%)

AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
S. aureus	3	3 (100%)
Streptococcus spp.	1	1 (100%)
S. pyogenes	1	1 (100%)
S. pneumoniae	2	2 (100%)

AMPICILLIN-RESISTANT ORGANISMS	No.	ERADICATED	NOT ERADICATED
Klebsiella spp.	1		1 (100%)

One patient developed a superinfection with resistant organisms during treatment.

SAFETY
No. of Patients: 15
No. with Local Side Effects: 1 (6.7%)
No. with Systemic Side Effects: 3 (20%)

LOCAL SIDE EFFECTS
Thrombophlebitis - 1 (6.7%)

SYSTEMIC SIDE EFFECTS
Nausea - 1 (6.7%)
Diarrhea - 1 (6.7%)
Rash - 1 (6.7%)

ABNORMAL LABORATORY TESTS

Increased eosinophils	- 1
Increased AST	- 1
Increased ALT	- 2
Increased alk. phosphatase	- 1
Increased gamma GT	- 2

24- Protocol #87-1
Title: An Open, Non-Comparative Study of the Efficacy and Safety of Sulbactam Plus Ampicillin in the Treatment of Urinary Tract Infections

Investigator: Professor Dr. A. Taupitz, Stadt. Krankenhaus, Kaiserslautern, W. Germany

Study Design:
Open, non-comparative study designed to determine the efficacy and safety of sulbactam in combination with ampicillin in the treatment of urinary tract infections caused by pathogens potentially resistant to ampicillin.

Patients
Twenty adult patients with complicated urinary tract infections were enrolled in this study.

Demographic Summary
Age (years)
Range: 17-86
Mean: 49.1

Sex
Male: 10
Female: 10

Dose and Route of Administration
Eighteen patients received sulbactam 1.5 g daily (500 mg tid) plus ampicillin 3.0 g daily (1.0 g tid). One patient received sulbactam 1.5 g daily (500 mg tid) plus ampicillin 1.5 g daily (500 mg tid), and a further patient was treated with sulbactam 2.0 g daily (500 mg qid) plus ampicillin 4.0 g daily (1.0 g qid).
All patients received the drugs by intravenous infusion.

Duration of Treatment
The duration of treatment ranged from 7 to 17 days with a mean duration of 9.3 days.

EVALUATION

EFFICACY
No. of Cases Evaluable: 5
No. of Cases Unevaluable: 15

Reasons Cases Unevaluable
No urine colony count - 1
Urine colony count less than 10^5 - 3
Duration of treatment not indicated - 1
No post-treatment culture - 10

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE	IMPROVE
UTI (Complicated)			
Cystitis	2		2
Pyelonephritis	3	2	1
TOTAL	5	2 (40%)	3 (60%)

AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
E. coli	3	3 (100%)
P. mirabilis	1	1 (100%)
Enterococcus	1	1 (100%)
E. cloacae	1	1 (100%)
E. hafniae	1	1 (100%)
Klebsiella spp.	1	1 (100%)

SAFETY
There were no treatment-related side effects reported.

ABNORAMAL LABORATORY TESTS
Increased AST - 1
Increased ALT - 1

25- Protocol #89-1
Title: An Open, Non-Comparative Study of the Efficacy, Safety and Pharmacokinetics of Sulbactam Plus Ampicillin in Urinary Tract Infections in Children.

Investigator: Dr. O. Johansson, Malmö Allmänna Hospital, Malmö, Sweden

Study Design
Open, non-comparative study designed to study the efficacy, safety and pharmacokinetics of a combination of sulbactam and ampicillin in a 1:2 ratio in children with urinary tract infections.

Patients
Four infants with a clinical diagnosis of urinary tract infection were entered in this study.

Demographic Summary

Age

11 months - 2 patients
17-18 months - 2 patients

Sex

Male: 1
Female: 3

Dose and Route of Administration

All patients received sulbactam at approximately 100 mg/kg (300-350 mg doses) in combination with ampicillin in a 1:2 ratio, in divided doses by I.V. bolus injection every 8 hours.
Two children continued treatment with sultamicillin suspension.

Duration of Treatment

The duration of parenteral treatment ranged from 2-3 days with a mean duration of 2.8 days.

EVALUATION

EFFICACY

No. of Cases Evaluable: 1
No. of Cases Unevaluable: 3

Reasons Cases Unevaluable

No pre-treatment pathogen - 1
No urine culture done before parenteral therapy changed to oral therapy - 1
Treatment discontinued due to rash - 1

RESULTS

INFECTION	No.	CLINICAL RESPONSE CURE
UTI (Uncomplicated)	1	1 (100%)

AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED
E. coli	1	1 (100%)

SAFETY

No. of Patients - 4
No. with Local Side Effects - 0
No. with Systemic Side Effects - 1

SYSTEMIC SIDE EFFECT

Rash - 1 (25%)

ABNORMAL LABORATORY TESTS

No abnormalities attributable to sulbactam : ampicillin were reported.

Pharmacokinetics

Results have been summarized under Metabolism and Pharmacokinetic Studies.

26- Protocol #93-1

Title: An Open, Non-Comparative Study : A Combination of Sulbactam with Ampicillin Followed by Oral Sultamicillin Therapy in Pediatric Patients

Investigator: Dr. Ph. Reinert, Centre Hospitalier Intercommunal de Creteil, Creteil, France

Study Design:
Open, non-comparative study of the efficacy and safety of sulbactam plus ampicillin followed by oral sultamicillin in the treatment of pediatric patients with infections caused by pathogens potentially resistant to ampicillin.

Patients
Nineteen children with acute urinary tract infections were enrolled in this study.

Demographic Summary

Age	
7 months	- 2 patients
1 - 2 years	- 9 patients
3 - 5 years	- 4 patients
7 - 9 years	- 2 patients
11 -12 years	- 2 patients

Sex
Male - 4 patients
Female - 15 patients

Dose and Route of Administration
Sulbactam 36-109.5 mg/kg/day (mean 80.7) was given in conjunction with ampicillin in a 1:2 ratio in divided doses every 6 hours by intravenous injection.
Three children, who were discontinued from treatment after 24 hours when an ampicillin-sensitive pathogen was identified, received only parenteral therapy. The remainder received oral sultamicillin following parenteral therapy.

Duration of Parenteral Therapy
The duration of therapy was 1 day in 17 patients and 2 days in 2 patients.

EVALUATION

EFFICACY
No. of Cases Evaluable - 0
No. of Cases Unevaluable - 19

Reasons Cases Unevaluable
No pre-treatment pathogen - 1
Treatment was discontinued after 24 hours when an ampicillin-sensitive organism was identified - 3
Duration of parenteral treatment 1-2 days then followed by oral sultamicillin - 15

SAFETY
There were no local or systemic side effects during the period of parenteral therapy.

ABNORMAL LABORATORY TESTS
Increased eosinophils - 2
Increased AST - 2

These abnormal laboratory test values occurred while patients were receiving sultamicillin; therefore, it is not possible to asssess whether they were related to sulbactam/ampicillin or to sultamicillin.

27- Protocol #98-1
Title: An Open Study to Asses the Efficacy of Sulbactam Plus Ampicillin in the Treatment of Acute Uncomplicated Gonorrhea

Investigators: Dr. A.G. Lawrence, MBBChir and Dr. E.T. Houang, MBChB, MRCPath, John Hunter Clinic, St. Stephen's Hospital, London.

Study Design: Open, non-comparative study of a single dose of a 1:2 ratio of sulbactam : ampicillin in the treatment of patients with acute uncomplicated gonorrhea.

Patients
A total of 101 patients, 73 males and 28 females, were enrolled in the study.

Demographic Summary
Age (years)
Range: 18-54
Mean: 25.8

Sex
Male: 73
Female: 28

Dose and Route of Administration
All patients were treated with an intramuscular injection of sulbactam 1 g plus ampicillin 2 g, dissolved in 6.4 ml of 0.5% lignocaine, together with oral probenecid 1 g.

EVALUATION

EFFICACY
No. of Cases Evaluable - 83 (M-58, F-25)
No. of Cases Unevaluable - 18

Reasons Cases Unevaluable
Negative pre-treatment culture - 9
No follow-up - 9

RESULTS

INFECTION	MALES			FEMALES	
	CLINICAL RESPONSE			CLINICAL RESPONSE	
Uncomplicated gonorrhea	No.	CURE	FAIL	No.	CURE
	58	57(98.3%)	1 (1.7%)	25	25 (100%)
		BACTERIOLOGIC RESPONSE		BACTERIOLOGIC RESPONSE	
ORGANISM	No.*	ERADICATED	NOT ERAD	No.	ERADICATED
AMPICILLIN-SENSITIVE N. gonorrhoeae	57	56 (98.2%)	1 (1.8%)	25	25 (100%)
AMPICILLIN-RESISTANT N. gonorrhoeae	1	1 (100%)			

No.* = No. of patients with infection

Bacteriologic Evaluation According to Site of Infection

SITE OF INFECTION	No.	No. ERADICATED
Urethra	60	60 (100%)
Cervix	23	23 (100%)
Rectum	19	18 (94.7%)
Throat	4	4 (100%)

Two patients cured at first follow-up admitted further sexual intercourse with infected partners and were thus deemed reinfected at second follow-up.

SAFETY

No. of Patients - 101
No. with Local Side Effects - 1
No. with Systemic Side Effects - 12

LOCAL SIDE EFFECTS

Pain at I.M injection site - 1

SYSTEMIC SIDE EFFECTS

Rash - 1
Diarrhea - 5
Fatigue/Malaise - 3
Chills - 1
Headache - 1

Abnoraml Laboratory Tests

Increased AST - 3
Increased bilirubin - 1
Increased creatinine - 1

Summary of Open, Noncomparative Studies
(European)

No. of Studies: 27

No. of Investigators: 31

	Adults	Children	Total
No. of Patients	464	40	504

	Adults	Children
Age Range	13-96	7 - 11 months - 5
		1 - 2 years - 19
		3 - 6 years - 7
		7 - 10 years - 7
		11 - 12 years - 2

Sex
Male - 280
Female - 224

Dose (Sulbactam : Ampicillin)

Adults	No.
500 : 1000 q12h	20
500 : 2000 q12h	1
1000 : 1000 q12h	13
500 : 500 q8h	54
500 : 1000 q8h	30
500 : 2000 q8h	27
500 : 5000 q8h	9
1000 : 1000 q8h	3
1000 : 2000 q8h	39
250 : 500 q6h	8
500 : 500 q6h	45
500 : 1000 q6h	67
1000 : 1000 q6h	45
500 : 1000 q4h	1
1000 : 1000 q4h	1
1000 : 2000 (single dose)	101

Children	No.
250 : 500 q6h	2
500 : 1000 q6h	1
Sulb 50 mg/kg/day	14
Amp 100 mg/kg/day	10
Amp 150 mg/kg/day	4
Sulb 100 mg/kg/day Amp 200 mg/kg/day	4
Sulb 36-109.5 mg/kg/day (mean 80.7) Amp 1:2 ratio	19

Route of Administration	Adults	Children
IV infusion	135	0
IV injection	105	40
IM injection	190	0
IV + IM	34	0

EFFICACY EVALUATION

ADULTS: No. of Cases Evaluable: 253

INFECTION		CLINICAL RESPONSE		
UNCOMPLICATED UTI	No.	CURE	IMPROVE	FAIL
Cytitis	11	9 (81.8%)	2 (18.2%)	
Pyelonephritis	11	11 (100%)		
Unspecified •	11	2 (18.2%)	8 (72.7%)	1 (9.1%)
TOTAL	33	22 (66.7%)	10 (30.3%)	1 (3%)
COMPLICATED UTI				
Cytitis	3	1 (33.3%)	2 (66.7%)	
Pyelonephritis	5	4 (80%)	1 (20%)	
Unspecified	5	1 (20%)	4 (80%)	
TOTAL	13	6 (46.2%)	7 (53.8%)	

table continued

INFECTION		CLINICAL RESPONSE		
LOWER RESPIRATORY	No.	CURE	IMPROVE	FAIL
Bronchitis	43	13 (30.2%)	27 (62.8%)	3 (7%)
Pneumonia	12	7 (58.3%)	5 (41.7%)	
Bronchopneumonia	7	2 (28.6%)	5 (71.4%)	
Empyema	1		1 (100%)	
TOTAL	63	22 (34.9%)	38 (60.3%)	3 (4.8%)

INFECTION		CLINICAL RESPONSE		
UPPER RESPIRATORY				
Epiglottic abscess	1	1 (100%)		
Pharyngeal abscess	1		1 (100%)	
Otitis media	1		1 (100%)	
Peritonsillar abscess	1		1 (100%)	
TOTAL	4	1 (25%)	3 (75%)	
SKIN & SKIN STRUCTURE				
Cellulitis	6		6 (100%)	
Abscess	7	3 (42.9%)	4 (57.1%)	
Wound infection	6	5 (83.3%)	1 (16.7%)	
Ulcer	1	1 (100%)		
TOTAL	20	9 (45%)	11 (55%)	
GYNECOLOGIC				
Pelvic abscess	3		3 (100%)	
Vaginal cuff infection	8	7 (87.5%)	1 (12.5%)	
Tubo-ovarian abscess	1		1 (100%)	
Endometritis	2	2 (100%)		
PID	1		1 (100%)	
TOTAL	15	9 (60%)	6 (40%)	
INTRA-ABOMINAL				
Peritonitis	9	5	2	2
Abscess	2	1	1	
Cholecystitis	1	1		
TOTAL	12	7 (58.3%)	3 (25%)	2 (16.7%)
BACTERIEMIA	10	8 (80%)	2 (20%)	

INFECTION		MALES CLINICAL RESPONSE		FEMALES CLINICAL RESPONSE	
UNCOMPLICATED	No.	CURE	FAIL	No.	CURE
GONORRHEA	58	57 (98.3%)	1 (1.7%)	25	25 (100%)

UNCOMPLICATED UTI AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
S. faecalis	1	1 (100%)	
E. coli	9	9 (100%)	
P. maltophilia	1	1 (100%)	

table continued

UNCOMPLICATED UTI

AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
E. coli	14	11 (78.6%)	3 (21.4%)
P. mirabilis	3	3 (100%)	
E. cloacae	1	1 (100%)	
K. pneumoniae	3	3 (100%)	
K. oxytoca	2	2 (100%)	

COMPLICATED UTI

AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
Enterococcus	1	1 (100%)	
E. coli	4	4 (100%)	
P. mirabilis	1	1 (100%)	
E. cloacae	1	1 (100%)	
E. hapniae	1	1 (100%)	
Klebsiella sp.	1	1 (100%)	

COMPLICATED UTI

AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
E. coli	4	4 (100%)	
P. mirabilis	2	2 (100%)	
P. stuartii	1	1 (100%)	

LOWER RESPIRATORY

AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
S. aureus	3	3 (100%)	
Streptococcus sp.	1	1 (100%)	
S. pyogenes	1	1 (100%)	
S. pneumoniae	11	11 (100%)	
B. catarrhalis	6	6 (100%)	
Haemophilis sp.	2	2 (100%)	
H. influenzae	13	10 (76.9%)	3 (23.1%)
H. parainfluenzae	6	2 (33.2%)	4 (66.7%)
E. coli	2		2 (100%)

LOWER RESPIRATORY

AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
S. aureus	8	7 (87.5%)	1 (12.5%)
B. catarrhalis	12	12 (100%)	
H. influenzae	5	5 (100%)	
H. parainfluenzae	3	3 (100%)	
E. coli	1	1 (100%)	
Klebsiella sp.	2	1 (50%)	1 (50%)
K. pneumoniae	2	1 (50%)	1 (50%)
K. oxytoca	1	1 (100%)	

table continued

UPPER RESPIRATORY AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
H. influenzae	1	1 (100%)	
E. coli	1		1 (100%)
S. epidermidis	1		1 (100%)

UPPER RESPIRATORY AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
K. pneumoniae	1	1 (100%)	

SKIN & SKIN STRUCTURE AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
S. aureus	3	3 (100%)	
S. epidermidis	2	1 (50%)	1 (50%)
Streptococcus sp.	1	1 (100%)	
S. milleri	1	1 (100%)	
S. pyogenes	2	2 (100%)	
S. sanguis	1	1 (100%)	
E. coli	1		1 (100%)
P. mirabilis	2	2 (100%)	
Citrobacter sp.	1	1 (100%)	

SKIN & SKIN STRUCTURE AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
S. aureus	9	9 (100%)	
S. epidermidis	1	1 (100%)	
M. morganii	2	2 (100%)	
Enterobacter sp.	1	1 (100%)	
K. pneumoniae	1	1 (100%)	
B. fragilis	1	1 (100%)	
B. melaninogenicus	1	1 (100%)	

GYNECOLOGIC AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
Enterococcus	2	2 (100%)	
E. coli	8	7 (87.5%)	1 (12.5%)
P. mirabilis	1	1 (100%)	
Bacteroides sp.	1	1 (100%)	

GYNECOLOGICN AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
E. coli	6	5 (83.3%)	1 (16.7%)
K. oxytoca	2	1 (50%)	1 (50%)
Peptococcus sp.	1	1 (100%)	
Bacteroides sp.	1	1 (100%)	
B. fragilis	1	1 (100%)	

table continued

INTRA-ABDOMINAL AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
Streptococcus sp.	5	5 (100%)	
E. coli	1	1 (100%)	
P. mirabilis	1	1 (100%)	

INTRA-ABDOMINAL AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
S. faecalis	1	1 (100%)	
E. coli	9	5 (55.6%)	4 (44.4%)
M. morganii	1	1 (100%)	
E. aerogenes	1	1 (100%)	
Klebsiella sp.	1		1 (100%)
K. oxytoca	1	1 (100%)	
B. fragilis	6	6 (100%)	
B. melaninogenicus	2	2 (100%)	

BACTEREMIA AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
Enterococcus	1	1 (100%)	
E. coli	3	3 (100%)	

BACEREMIA AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
S. aureus	2	2 (100%)	
E. coli	2	2 (100%)	
Klebsiella sp.	1	1 (100%)	
Y. enterocolitica	1	1 (100%)	

GONORRHEA		MALES		FEMALES	
AMPICILLIN-SENSITIVE		BACTERIOLOGIC RESPONSE			BACTERIOLOGIC RESPONSE
ORGANISMS	No.	ERADICATED	NOT ERAD	No.	ERADICATED
N. gonorrhoeae	57	56 (98.2%)	1 (1.8%)	25	25 (100%)

GONORRHEA AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERAD
N. gonorrhoeae	1	1 (100%)	

EFFICAC1 EVALUATION

CHILDREN: No. of Cases Evaluable - 14

INFECTION		CLINICAL RESPONSE		
UNCOMP-ICATED UTI	No.	CURE	IMPROVE	FAiL
Unspecified	6	6 (100%)		
COMPLICATED UTI				
Unspecified	4	3 (75%)		1 (25%)
SKIN & SKIN STRUCTURE				
Lymphadenitis	4	4 (100%)		

UNCOMPLICATED UTI AMPICILLIN-SENSITIVE ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
E. coli	1	1 (100%)	

UNCOMPLICATED UTI AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
E. coli	5	5 (100%)	

COMPLICATED UTI AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
E. coli	4	3 (75%)	1 (25%)

SKIN & SKIN STRUCTURE AMPICILLIN-RESISTANT ORGANISMS	No.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
S. aureus	4	4 (100%)	

SAFETY EVALUATION

	ADULTS	CHILDREN	TOTAL
No. of Patients	463	40	503
No. with Local Side Effects	68 (14.7%)	2 (5%)	70 (13.9%)
No. with Systemic Side Effects	29 (6.3%)	1 (2.5%)	30 (6%)
LOCAL SIDE EFFECTS			
Pain at IM injection site	37 (16.5%)	-	
Abscess at IM injection site	1 (0.4%)	-	
Pain at IV injection site	22 (8%)	2 (5%)	24 (7.6%)
Thrombophlebitis	8 (3%)	-	8 (2.5%)
SYSTEMIC SIDE EFFECTS			
Nausea	3 (0.6%)		3 (0.6%)
Vomiting	2 (0.4%)		2 (0.4%)
Diarrhea	11 (2.4%)		11 (2.2%)
Glossitis	1 (0.2%)		1 (0.2%)
Itching	2 (0.4%)		2 (0.4%)
Erythema	1 (0.2%)		1 (0.2%)
Rash	6 (1.3%)	1 (2.5%)	7 (1.4%)
Inguinal and facial swelling	1 (0.2%)		1 (0.2%)
Chills	1 (0.2%)		1 (0.2%)
Headache	2 (0.4%)		2 (0.4%)
Fatigue/Malaise	3 (0.6%)		3 (0.6%)
Vaginal candidiasis	1 (0.2%)		1 (0.2%)
Dysuria	1 (0.2%)		1 (0.2%)

ABNORMAL LABORATORY TESTS	ADULTS	CHILDREN	TOTAL
Decreased Hgb	8	0	8
Decreased Hct	7	0	7
Decreased RBCs	1	0	1
Decreased WBCs	1	0	1
Decreased neutrophils	1	1	2
Decreased platelets	2	0	2
Increased platelets	9	0	9
Increased eosinophils	11	3	14
Increased SGOT	29	3	32
Increased SGPT	15	1	16
Increased alk. phosphatase	9	0	9
Increased bilirubin	2	0	2
Increased GGT	2	0	2
Increased blood urea	3	0	3
Increased creatinine	3	0	3

Conclusions

These open, non-comparative studies were conducted to determine the efficacy and safety of sulbactam plus ampicillin in the treatment of patients with infections caused by pathogenic bacteria susceptible to the combination treatment regimen.
A total of 504 patients, 464 adults and 40 children, were enrolled in these studies.

Evaluation of drug efficacy was assessed in 253 adults and in 14 children. Evaluation of drug safety was assessed in 503 patients.

In adult patients, a satisfactory clinical response (cure/improve) was achieved in 32/33 (97%) patients with uncomplicated UTI, in 13/13 (100%) with complicated UTI, in 60/63 (95%) with lower respiratory infections, 4/4 (100%) with upper respiratory infections, in 20/20 (100%) with skin and skin structure infections, 15/15 (100%) with gynecologic infections, in 10/12 (83%) with intra-abdominal infections, in 10/10 (100%) with bacteremia and in 82/83 (98.8%) with uncomplicated gonorrhea.

In patients with uncomplicated UTIs, sulbactam/ ampicillin eradicated 11/11 (100%) ampicillin-sensitive organisms and 20/23 (87%) ampicillin-resistant organisms; in complicated UTIs eradicated 9/9 (100%) ampicillin-sensitive organisms and 7/7 (100%) ampicillin-resistant organisms; in lower respiratory infections eradicated 36/45 (80%) ampicillin-sensitive organisms and 31/34 (91%) ampicillin-resistant organisms; in upper respiratory infections eradicated 1/3 (33%) ampicillin sensitive organisms and 1/1 (100%) ampicillin-resistant organisms; in skin and skin structure infections eradicated 12/14 (86%) ampicillin-sensitive organisms and 16/16 (100%) ampicillin-resistant organisms; in gynecologic infections eradicated 11/12 (92%) ampicillin-sensitive oraganisms and 9/11 (82%) ampicillin-resistant organisms; in intra-abdominal infections eradicated 7/7 (100%) ampicillin-sensitive and 17/22 (77%) ampicillin-resistant organisms; in bacteremias eradicated 4/4 (100%) ampicillin-sensitive and 6/6 (100%) ampicillin-resistant organisms and in uncomplicated gonorrhea eradicated 81/82 (99%) ampicillin-sensitive and 1/1 (100%) ampicillin-resistant N. gonorrhoeae.

In children, a satisfactory clinical response was achieved in 6/6 (100%) patients with uncomplicated UTI, in 3/4 (75%) with complicated UTI and in 4/4 (100%) with skin and skin structure infections.

In patients with uncomplicated UTI, sulbactam/ampicillin eradicated 1/1 (100%) ampicillin-sensitive E. coli and 5/5 (100%) ampicillin-resistant E. coli; in complicated UTI eradicated 3/4 (75%) ampicillin-resistant E. coli and in skin and skin structure infections eradicated 4/4 (100%) ampicillin-resistant S. aureus.

In adults, local side effects were reported in 68/463 (14.7%) patients. These were pain at IV injection site, 22/273 (8%); thrombophlebitis, 8/273 (3%); pain at IM injection site, 37/224 (17%), and abscess at IM injection site, 1/224 (0.4%).
In children, local side effects (pain at IV injection site) were reported in 2/40 (5%).

Systemic side effects were reported in 29/463 (6.3%) adults and in 1/40 (2.5%) children. Rash and diarrhea were the most commonly reported side effects.

The most commonly reported abnormal laboratory tests were eosinophilia and increased liver function test values.

Overall Summary of the Efficacy and Safety of Sulbactam/Ampicillin in Comparative and Non-Comparative Studies

	Comparative	Non-Comparative
No. of Studies	13	35

DEMOGRAPHIC SUMMARY

	ADULTS	CHILDREN	TOTAL
No. of Patients	1061	91	1152

	ADULTS	CHILDREN
AGE RANGE	13-99	1 - 2 mos. - 2 patients
		3 -11 mos. - 14 patients
		1 - 2 yrs. - 35 patients
		3 -10 yrs. - 38 patients
		11 -12 yrs. - 2 patients

SEX
Male - 636
Female - 516

ROUTE OF DRUG ADMINISTRATION

	ADULTS	CHILDREN
IV	832	91
IM	195	-
IV + IM	34	-

EVALUATION

EFFICACY

	ADULTS	CHILDREN	TOTAL
No. of Cases Evaluable	527	45	572

RESULTS

INFECTION	ADULTS CLINICAL RESPONSE No.	ADULTS CLINICAL RESPONSE CURE/IMP	CHILDREN CLINICAL RESPONSE No.	CHILDREN CLINICAL RESPONSE CURE/IMP	TOTAL CLINICAL RESPONSE No.	TOTAL CLINICAL RESPONSE CURE/IMP
UPPER RESPIRATORY	4	4 (100%)	19	19 (100%)	23	23 (100%)
LOWER RESPIRATORY	74	71 (96%)	-		74	71 (96%)
SKIN & SKIN STRUCTURE	151	144 (95%)	4	4 (100%)	155	148 (95%)
UNCOMPLICATED UTI	35	34 (97%)	6	6 (100%)	41	40 (98%)
COMPLICATED UTI	13	13 (100%)	4	3 (75%)	17	16 (94%)
INTRA-ABDOMINAL	113	103 (91%)	-		113	103 (91%)
GYNECOLOGIC	40	38 (95%)	-		40	38 (95%)
GONORRHEA	83	83 (100%)	-		83	83 (100%)
BACTEREMIA	10	10 (100%)	-		10	10 (100%)
BONE/JOINT	4	4 (100%)	1	1 (100%)	5	5 (100%)
MENINGITIS	-		11	10 (91%)	11	10 (91%)

UPPER RESPIRATORY AMPICILLIN-SENSITIVE ORGANISMS	ADULTS BACTERIOLOGIC RESPONSE No.	ADULTS BACTERIOLOGIC RESPONSE ERADICATED	CHILDREN BACTERIOLOGIC RESPONSE No.	CHILDREN BACTERIOLOGIC RESPONSE ERADICATED	TOTAL BACTERIOLOGIC RESPONSE No.	TOTAL BACTERIOLOGIC RESPONSE ERADICATED
S. epidermidis	1	0 (0%)	-	-	1	0 (0%)
H. influenzae	1	1 (100%)	13	13 (100%)	14	14 (100%)
E. coli	1	0 (0%)	-	-	1	0 (0%)

UPPER RESPIRATORY AMPICILLIN-RESISTANT ORGANISMS	No.	ERADICATED	No.	ERADICATED	No.	ERADICATED
H. influenzae	-	-	6	6 (100%)	6	6 (100%)
K. pneumoniae	1	1 (100%)	-	-	1	1 (100%)

LOWER RESPIRATORY AMPICILLIN-SENSITIVE ORGANISMS	No.	ERADICATED	No.	ERADICATED	No.	ERADICATED
S. aureus	3	3 (100%)	-			
Streptoccus sp.	2	2 (100%)	-			
S. pyogenes	1	1 (100%)	-			
S. pneumoniae	14	14 (100%)	-			
H. influenzae	17	14 (82%)	-			
Haemophilus sp.	2	2 (100%)	-			
H. parainfluenzae	7	3 (43%)	-			
B. catarrhalis	6	6 (100%)	-			
E. coli	3	1 (33%)	-			
P. mirabilis	1	0 (0%)	-			
Peptostreptococcus sp.	1	1 (100%)	-			
F. nucleatum	1	1 (100%)	-			
Bacteroides sp.	2	2 (100%)	-			

LOWER RESPIRATORY AMPICILLIN-RESISTANT ORGANISMS	ADULTS BACTERIOLOGIC RESPONSE		CHILDREN BACTERIOLOGIC RESPONSE	
	No.	ERADICATED	No.	ERADICATED
S. aureus	8	7 (88%)	-	
H. influenzae	7	7 (100%)	-	
H. parainfluenzae	3	3 (100%)	-	
B. catarrhalis	12	12 (100%)	-	
E. coli	3	3 (100%)	-	
M. morganii	1	0 (0%)	-	
A. calcoaceticus	1	1 (100%)	-	
A. anitratus	1	1 (100%)	-	
Klebsiella sp.	2	1 (50%)	-	
K. pneumoniae	2	1 (50%)	-	
K. oxytoca	1	1 (100%)	-	

SKIN & SKIN STRUCTURE AMPICILLIN-SENSITIVE ORGANISMS	ADULTS BACTERIOLOGIC RESPONSE		CHILDREN BACTERIOLOGIC RESPONSE	
	No.	ERADICATED	No.	ERADICATED
Coagulase neg. staph.	4	4 (100%)	-	
S. aureus	13	13 (100%)	-	
S. epidermidis	4	2 (50%)	-	
Streptococcus sp.	10	9 (90%)	-	
S. pyogenes	30	30 (100%)	-	
Group B strep.	2	2 (100%)	-	
S. milleri	1	1 (100%)	-	
S. sanguis	1	1 (100%)	-	
S. faecalis	7	6 (86%)	-	
Enterococci	4	4 (100%)	-	
Group D strep	7	7 (100%)	-	
Corynebacterium sp.	1	0 (0%)	-	
Bacillus sp.	2	2 (100%)	-	
H. parainfluenzae	1	1 (100%)	-	
E. coli	14	12 (86%)	-	
P. mirabilis	14	13 (93%)	-	
E. cloacae	3	3 (100%)	-	
K. pneumoniae	1	1 (100%)	-	
Citrobacter sp.	2	2 (100%)	-	
A. calcoaceticus	2	2 (100%)	-	
Salmonella type B	1	1 (100%)	-	
Peptococcus sp.	3	3 (100%)	-	
Peptostreptoccus sp.	2	2 (100%)	-	
Propionibacterium sp.	1	1 (100%)	-	
Bacteroides sp.	2	2 (100%)	-	
B. fragilis	1	1 (100%)	-	
B. melaninogenicus	1	1 (100%)	-	

SKIN & SKIN STRUCTURE AMPICILLIN-RESISTANT ORGANISMS		...LOGIC ...SE ...RADICATED	CHILDREN BACTERIOLOGIC RESPONSE No.	ERADICATED	TOTAL BACTERIOLOGIC RESPONSE No.	ERADICATED
Coagulase neg. staph.	2	1 (50%)	-			
Staphyloccus sp.	2	2 (100%)	-			
S. aureus	67	61 (91%)	4	4	71	65 (92%)
S. epidermidis	4	4 (100%)	-			
S. liquefaciens	1	1 (100%)	-			
E. coli	6	5 (83%)	-			
P. mirabilis	4	3 (75%)	-			
P. vulgaris	2	2 (100%)	-			
Providencia sp.	2	1 (50%)	-			
M. morganii	4	4 (100%)	-			
Enterobacter sp.	2	2 (100%)	-			
E. coloacae	4	4 (100%)	-			
Acinetobacter sp.	1	1 (100%)	-			
A. calcoaceticus	6	6 (100%)	-			
Achromobacter sp.	1	1 (100%)	-			
Klebsiella sp.	1	1 (100%)	-			
K. pneumoniae	5	4 (80%)	-			
K. ozaenae	2	2 (100%)	-			
C. diversus	1	1 (100%)	-			
C. freundii	1	1 (100%)	-			
Flavobacterium sp.	1	1 (100%)	-			
S. marcescens	1	1 (100%)	-			
P. aeruginosa	4	1 (25%)	-			
A. hydrophilia	1	1 (100%)	-			
C. perfringens	1	1 (100%)	-			
B. melaninogenicus	1	1 (100%)	-			
B. fragilis	6	6 (100%)	-			

URINARY TRACT AMPICILLIN-SENSITIVE ORGANISMS	ADULTS BACTERIOLOGIC RESPONSE		CHILDREN BACTERIOLOGIC RESPONSE		TOTAL BACTERIOLOGIC RESPONSE	
	No.	ERADICATED	No.	ERADICATED	No.	ERADICATED
S. faecalis	1	1 (100%)	-			
Enterococcus	1	1 (100%)	-			
E. coli	14	14 (100%)	1	1 (100%)	15	15 (100%)
P. mirabilis	1	1 (100%)	-			
E. cloacae	1	1 (100%)	-			
E. hafniae	1	1 (100%)	-			
Klebsiella sp.	1	1 (100%)	-			
P. maltophilia	1	1 (100%)	-			

URINARY TRACT AMPICILLIN-RESISTANT ORGANISMS	No.	ERADICATED	No.	ERADICATED	No.	ERADICATED
E. coli	19	15 (79%)	9	8 (89%)	28	23 (82%)
P. mirabilis	5	5 (100%)	-			
P. stuartii	1	1 (100%)	-			
E. cloacae	1	1 (100%)	-			
K. pneumoniae	3	3 (100%)	-			
K. oxytoca	2	2 (100%)	-			

INTRA-ABDOMINAL AMPICILLIN-SENSITIVE ORGANISMS	ADULTS BACTERIOLOGIC RESPONSE		CHILDREN
	No.	ERADICATED	No.
S. epidermidis	1	1 (100%)	–
Streptococcus sp.	13	12 (92%)	–
S. viridans	9	9 (100%)	–
S. pyogenes	1	1 (100%)	–
Group D strep.	2	2 (100%)	–
S. faecalis	3	3 (100%)	–
Enterococcus	1	1 (100%)	–
E. coli	39	37 (95%)	–
P. mirabilis	2	2 (100%)	–
C. freundii	2	2 (100%)	–
Enterobacter sp.	1	1 (100%)	–
Klebsiella sp.	1	0 (0%)	–
K. oxytoca	1	1 (100%)	–
C. perfringens	1	1 (100%)	–
Bifidobacterium sp.	1	1 (100%)	–
Eubacterium sp.	4	4 (100%)	–
Propionibacterium sp.	2	2 (100%)	–
P. magnus	3	3 (100%)	–
Peptococcus sp.	1	1 (100%)	–
Peptostreptococcus sp.		1 (100%)	–
Lactobacillus sp.	4	4 (100%)	–
Fusobacterium sp.	1	1 (100%)	–
F. nucleatum	2	2 (100%)	–
Bacteroides sp.	5	5 (100%)	–
B. fragilis	10	10 (100%)	–
B. distasonis	4	4 (100%)	–
B. melaninogenicus	1	1 (100%)	–
B. ruminicola	1	0 (0%)	–

INTRA-ABDOMINAL AMPICILLIN-RESISTANT ORGANISMS	ADULTS BACTERIOLOGIC RESPONSE No.	ERADICATED	CHILDREN No.
S. aureus	1	1 (100%)	-
S. epidermidis	2	2 (100%)	-
S. faecalis	1	1 (100%)	-
E. coli	52	46 (88%)	-
Enterobacter sp.	2	2 (100%)	-
E. aerogenes	2	2 (100%)	-
E. cloacae	3	3 (100%)	-
Klebsiella sp.	4	2 (50%)	-
K. pneumoniae	5	5 (100%)	-
K. oxytoca	4	4 (100%)	-
M. morganii	1	1 (100%)	-
Eubacterium sp.	1	1 (100%)	-
Citrobacter sp.	1	1 (100%)	-
C. freundii	3	3 (100%)	-
A. faecalis	1	1 (100%)	-
Aeromonas sp.	1	1 (100%)	-
P. aeruginosa	13	13 (100%)	-
Clostridium sp.	1	1 (100%)	-
Bacteroides sp.	19	19 (100%)	-
B. fragilis	39	38 (97%)	-
B. distasonis	11	11 (100%)	-
B. corrodens	1	1 (100%)	-
B. melaninogenicus	2	2 (100%)	-

GYNECOLOGIC AMPICILLIN-SENSITIVE ORGANISMS	No.	ADULTS BACTERIOLOGIC RESPONSE ERADICATED
Streptococcus sp.	1	1 (100%)
S. viridans	1	1 (100%)
S. pyogenes	1	1 (100%)
Group B strep.	6	6 (100%)
Enterococci	3	3 (100%)
Diphtheroids	1	1 (100%)
E. coli	10	9 (90%)
P. mirabilis	1	1 (100%)
N. gonorrhoeae	4	4 (100%)
G. vaginalis	8	8 (100%)
Peptococcus sp.	1	1 (100%)
Peptostreptococcus	3	3 (100%)
Bacteroides sp.	1	1 (100%)

GYNECOLOGIC AMPICILLIN-RESISTANT ORGANISMS	No.	ADULTS BACTERIOLOGIC RESPONSE ERADICATED
Gamma strep.	1	1 (100%)
S. viridans	1	1 (100%)
S. epidermidis	1	1 (100%)
E. coli	8	7 (88%)
K. oxytoca	3	2 (67%)
N. gonorrhoeae	2	2 (100%)
Peptococcus sp.	1	1 (100%)
Bacteroides sp.	1	1 (100%)
Bacteroides fragilis	6	6 (100%)

GONORRHEA AMPICILLIN-SENSITIVE ORGANISMS	No.	ADULTS BACTERIOLOGIC RESPONSE ERADICATED
N. gonorrhoeae	82	81 (99%)

GONORRHEA AMPICILLIN-RESISTANT ORGANISMS	No.	ERADICATED
N. gonorrhoeae	1	1 (100%)

BACTEREMIA AMPICILLIN-SENSITIVE ORGANISMS	No.	ERADICATED
Enterococcus	1	1 (100%)
E. coli	3	3 (100%)

BACTEREMIA AMPICILLIN-RESISTANT ORGANISMS	No.	ERADICATED
S. aureus	2	2 (100%)
E. coli	2	2 (100%)
Klebsiella sp.	1	1 (100%)
Y. enterocolitica	1	1 (100%)

BONE/JOINT AMPICILLIN-SENSITIVE ORGANISMS	ADULTS BACTERIOLOGIC RESPONSE No.	Eradicated	CHILDREN BACTERIOLOGIC RESPONSE No.	Eradicated
S. faecalis	1	1 (100%)		
H. influenzae			1	1 (100%)

BONE/JOINT AMPICILLIN-RESISTANT ORGANISMS	No.	Eradicated	No.	Eradicated
S. aureus	3	2 (67%)		
S. epidermidis	1	1 (100%)		

MENINGITIS AMPICILLIN-SENSITIVE ORGANISMS	No.	Eradicated	No.	Eradicated
S. pneumoniae			2	2 (100%)
H. influenzae			6	6 (100%)
Neisseria sp.			1	1 (100%)

MENINGITIS AMPICILLIN-RESISTANT ORGANISMS	No.	Eradicated	No.	Eradicated
H. influenzae			2	2 (100%)

SAFETY

	ADULTS	CHILDREN	TOTAL
No. of Patients	1060	91	1151
No. with LOCAL SIDE EFFECTS	87 (8.2%)	3 (3.3%)	90 (7.8%)
No. with SYSTEMIC SIDE EFFECTS	65 (6.1%)	2 (2.2%)	67 (5.8%)
LOCAL SIDE EFFECTS			
Pain IV injection site	27/866 (3.1%)	3/91 (3.3%)	30/957 (3.1%)
Thrombophlebitis	23/866 (2.7%)		
Pain IM injections site	37/229 (16.2%)		
Abscess at IM site	1/229 (0.4%)		

SYSTEMIC SIDE EFFECTS	ADULTS	CHILDREN	TOTAL
Itching	6 (0.6%)		
Rash	13 (1.2%)	1 (1.1%)	14 (1.2%)
Erythema	1 (0.1%)		
Headache	2 (0.2%)		
Flatulence	1 (0.1%)		
Abdominal distension	1 (0.1%)		
Nausea	5 (0.5%)		
Vomiting	4 (0.4%)		
Diarrhea	30 (2.8%)		
Glossitis	1 (0.1%)		
Oral candidiasis	1 (0.1%)		
Vaginal candidiasis	2 (0.2%)		
Yeast infection	1 (0.1%)		
Urine retention	1 (0.1%)		
Dysuria	1 (0.1%)		
Edema	1 (0.1%)		
Inguinal and facial swelling	1 (0.1%)		
Chills	1 (0.1%)		
Chest pain	2 (0.2%)		
Tightness in throat and substernal pain	1 (0.1%)		
Fatigue/malaise	3 (0.3%)		
Epistaxis	1 (0.1%)		
Bleeding from oral and rectal mucosa and venipuncture site		1 (1.1%)	1 (0.1%)

ABNORMAL LABORATORY TESTS	No. ABNORMAL/No. DETERMINED	
Decreased Hgb	40/1071	(3.7%)
Decreased Hct	37/1047	(3.5%)
Decreased RBCs	18/978	(1.8%)
Decreased WBCs	2/1071	(0.2%)
Decreased neutrophils	5/854	(0.6%)
Decreased lymphocytes	8/860	(0.9%)
Increased lymphocytes	2/860	(0.2%)
Increased monocytes	11/857	(1.3%)
Increased basophils	5/833	(0.6%)
Increased eosinophils	51/851	(5.9%)
Increased platelets	21/721	(2.9%)
Decreased platelets	3/721	(0.4%)
Decreased serum albumin	8/150	(5.3%)
Decreased total proteins	4/150	(2.7%)
Increased SGOT	102/1004	(10.2%)
Increased SGPT	84/804	(10.4%)
Increased alk. phosphatase	49/1020	(4.8%)
Increased LDH	40/258	(15.5%)
Increased bilirubin	7/975	(0.7%)
Increased GGT	4/75	(5.3%)
Increased BUN	3/510	(0.6%)
Increased creatinine	4/1024	(0.4%)
Increased uric acid	2/157	(1.3%)
Hyaline casts in urine	2/731	(0.3%)
RBCs in urine	4/731	(0.5%)
Increased blood urea	3/391	(0.8%)

Deaths

A total of 39 deaths occurred ammong the patients treated with sulbactam/ampicillin.

None of the deaths was considered to be drug related.

Overall Conclusions

Results obtained in clinical studies conducted by well qualified investigators demonstrate that Unasyn (sulbactam/ampicillin) is safe and effective in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

1- Lower Respiratory Infections caused by beta-lactamase producing strains of Staphylococcus aureus*, Branhamella catarrhalis and Haemophilus influenzae*.

2- Skin and Skin Structure Infections cause by beta-lactamase producing strains of Staphylococcus aureus, Escherichia coli*, Proteus species*, Enterobacter species*, Acinetobacter calcoaceticus*, Klebsiella species* (including K. pneumoniae*), and Bacteroides species* (including B. fragilis*).

3- Urinary Tract Infections (complicated and uncomplicated) caused by beta-lactamase producing strains of Escherichia coli, Proteus mirabilis* and Klebsiella species* (including K. pneumoniae*).

4- Intra-Abdominal Infections caused by beta-lactamase producing strains of Escherichia coli, Enterobacter species*, Klebsiella species (including K. pneumoniae*) and Bacteroides species (including B. fragilis).

5- Gynecologic Infections caused by beta-lactamase producing strains of Escherichia coli* and Bacteroides* species (including B. fragilis*).

The data are not adequated to support the efficacy of Unasyn (sulbactam/ampicillin) in the treatment of bacterial septicemia, upper repiratory, bone and joint, and central nervous system infections. The data are considered also inadequate to support the use of Unasyn in children.

* Efficacy for this organism in this organ system was demonstrated in less than 10 infections.

Review of Package Insert

The proposed package insert requires extensive revisions; therefore, its evaluation will be deferred until a meeting with other team reviewers and Pfizer's representatives is held in the near future.

Recommendations

Based on the data contained in Antibiotic Form 5 50-608, it is recommended that Unasyn (sulbactam/ampicillin) be approved for the indications listed under Overall Conclusions.

M S Albuerne, M.D.
M. S. Albuerne, M.D.

cc:
Orig NDA
ET 3/28/86
HFN-3[illegible], HFN-815, HFN-815/CSO, HFN-815/MSAlbuerne:bam:3/4/85:0750m

[illegible] 5 Mar 86

PHARM REVIEW

REVIEW AND EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

Form 5 - 50-608 (Original Submission, dated 4/18/85)

Date Review Completed: 9/5/85

Sponsor: Pfizer Central Research, Groton, Conn.

Drug: Trade Name: UNASYN®

Generic Name: Sulbactam Sodium/Ampicillin Sodium (ratio of 1:2)

Code Name: CP-45,899-2 (sulbactam Na)
CP-45,899 (sulbactam as free acid; equiv. to 91.4% Na salt)

Category: Antibiotic/Beta-Lactamase Inhibitor Combination

Dosage Form: Parenteral; vials containing sulbactam + ampicillin combination (1:2)

Sulbactam		Ampicillin
1000 mg	+	2000 mg
500 mg	+	1000 mg
250 mg	+	500 mg
125 mg	+	250 mg

The drug is to be supplied as sterile powder, to be reconstituted with specified volume of diluent.

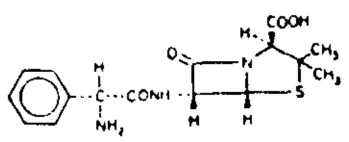
Proposed Dose

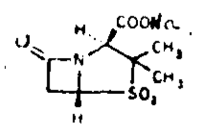
Adults: 1.5 to 3.0 g, q 6 h; total dose not to exceed 4 g/day (equiv. to 80 mpk of the combination in a 50 kg patient)

Children/infants/neonates: 150 mg/day

Structures

Ampicillin   sulbactam Sodium





Chemical Names

Sulbactam

1. 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-, 4,4-dioxide, sodium salt, (2S,cis)-

2. Sodium (2S,5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylate 4,4-dioxide.

Ampicillin

1. 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(amino-phenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt, [2S-[2α, 5α, 6β(S)*]]-

2. Monosodium (2S,5R,6R)-6-[(R)-2-amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.

3. Sodium (6R)-6-(α -phenyl-D-glyclamino)penicillinate

Acute Toxicity

Sulbactam Sodium (CP-45,899-2)

Acute Toxicity

Protocol #	Duration	Species	Route	Dose Levels* mg/kg/day	Findings
77-225-05	Acute-single dose LD_{50}	rats 10 males/ level/route	oral tube i.v.	>4 g/kg >3.4 g/kg	rats and mice – no mortality by oral route; considerable thirst and mild diarrhea regardless of route
		mice 10/sex/level	oral tube	>10 g/kg	mice – ataxia, decreased respiration, depression; maximum mortality in males by i.v. administration in 40 seconds
		10 males/level	i.v.	3.604 g/kg (LD_{50})	
77-225-20	Acute-single dose	rats neonatal 9-10 males/level	s.c.	1000, 2500, 5000	LD_{50} > 5000 mg/kg 5000 mg/kg – deaths in 2/9 in 7-8 days post partum: depression, weakness, failure to nurse, hypothermia 2500 mg/kg – slight depression 1000 mg/kg – asymptomatic
83-225-27 Sulbactam Sod.:Amp. Sod. 1:2	Acute-single dose	mice 5/sex/level	i.v.	625/1250 to 1875/3750	LD_{50} Males 1250/2500 - 1375/2750 mg/kg Females >1250/2500 mg/kg sulbactam/ ampicillin activity. 1875/3750 – 5/5 deaths, 1/2 to 3 minutes after dosing - clonic convulsions.
		rats 5/sex/level	i.v.	625/1250 to 1875/3750	LD_{50} Males ca 1875/3750 mg/kg Females >1875/3750 mg/kg Acute deaths following clonic convulsions.
83-225-29 Sulbactam/ Ampicillin 125/250 mg/ml	Acute-single dose venous irritation	rabbits 4M/2F	i.v.	1 ml	Mildly irritating.

* Doses expressed as free acid

Subacute/Chronic Toxicity

Intravenous Injection

1. Five-day (4-dose) IV Range Finding Study in Dogs with CP-2 Alone and in Combination with K Penicillin G: [Rpt. No. 77-225-08]

   Material Tested: CP-2 and Pfizerpen^R (Penicillin G)

   Animals: 1/sex/dose, Beagles

   Groups:

	Dose (mpk)	Conc'n.	Volume (ml/kg)
CP-2	1000	250	4.0
"	800	250	3.2
" /K Penicillin G	200/200	240/141	1.1/1.42
Controls	Sterile Saline	0.9% NaCl	4.0

N 50608 -4

All doses were injected IV @ 3-5 ml/min. via the cephalic vein. Dogs were dosed once daily for 4 consec. days.

Results: No mortality. Adverse clinical reactions to IV bolus injections manifestation of K^+ contents in K penicillin G were observed in the combo treated gp, and were a function of its rate of admin.

Clinical Pathology: Elevations in SGOT & SGPT observed in the combo gp were considered to be related to penicillin G admin. since no alterations in these enzymes occurred in either the LD or HD sulbactam (alone) gps.

Pathology: Gross & histopath. revealed no drug-related alterations, except reaction at the injection site.

2. One-month IV Study in Dogs with CP-2 Alone or in Combination with Penicillin G: [Rpt. No. 77-225-10]

Material Tested: CP-2; buffered Pfizerpen^R; Polycillin-N^R

Animals: 6/sex/dose, Beagles

Treatment Groups

	Dose (mpk/day)	Conc'n (mg/ml)	Volume(ml/kg)
CP-2	800	250	3.2
"	400	250	1.6
"	200	250	0.8
" + Penicillin G	200/200	200/200	1.0
" + Ampicillin	200/200	200/200	1.0
Saline Controls			1.0

All dogs were dosed once daily for 35 consec. days. The infusion rate was approx. 4 ml/min (sulbactam) & 2 ml/min (drug combo).

Results: One F dog from the penicillin G combo gp died on day 35; death was ascribed to dosing - both to K content and rapid delivery.

Clinical Signs: Dose-related soft stools, emesis in the penicillin G combo gp. Vital signs, EKGs & indirect systolic BP showed only normal variation. No drug-induced ocular lesions were reported.

Body Wts: Individual body wt losses were slight (1.0-2.4%).

Clin. Pathology: Stat. sig. elevation of alk. phos. (ALP) in HD & MD M and in MD F. Elevation of SGOT & SGPT were noted. Elevation in SGPT occurred in HD M on day 15 and in MD F on day 19. These were dose and time-related. No elevations at the LD in either sulbactam or sulbactam/ampicillin combo gp on day 29. Although there were also increases in prothrombin times in drug-treated gps compared to controls, all individual values were considered within normal limits (except 1 HD M).

Urinalysis: Negative for all dogs.

Gross & Histopathology

- Injection site reactions were mild to moderate.

- Dose-related hepatocellular "glycogenosis" was observed in all drug-treated dogs. The lesion, defined as "increased glycogen storage" in hepatocytes was characterized by redistribution of cellular glycogen into dense packets located peripherally in the hepatocytes. "The compartmentalization of hepatic intracellular glycogen constitutes a storage pattern that deviates from the normal diffuse intracellular storage of hepatic glycogen."

In further discussion of this lesion, the following is stated: "The only histologic indication of an adverse effect of this glycogenosis was widely scattered necrosis of individual hepatocytes in one (1/3) CP-45,899-2 high dose level male dog (Animal No. 731854). This dog also demonstrated the largest increase in SGPT (101 mU/ml), SGOT (74 mU/ml) and prothrombin times."

"The nature of the PAS positive deposits within the hepatocytes was investigated by enzyme histochemical techniques. The deposits appear to be glycogen which is abnormal in its histochemical morphology and its decreased susceptibility to enzyme digestion. The deposits are completely digested by malt diastase treatment."

3. 17-Day IV Infusion & Withdrawal Study of Sulbactam Na in Beagle Dogs: [Rpt. No. 78-225-13]

Objective: To determine reversibility of hepatic glycogenosis observed in the previous 1-month IV dog study.

Animals: Total of 8 Beagles (7-7.5 months old); 6 in expt 1; 2 in expt 2

Groups

	Dose	No. of dogs
CP-2	800 mpk	3M +3F (Biopsy on day 16)
Saline Controls	0	1M + 1F

Experimental Plan: Dogs were given IV infusion at approx. 4 ml/min., once daily for 17 consec. days. Two drug-treated M were killed on day 19 after 48-hr fast. The remaining 1 M & 3 F were killed on day 113/114 after 24-hr fast.

Results

Clinical Observations: No mortality

Clin. Pathology: Serum chem., hematology & urinalysis were performed twice on all dogs (once pretreatment; again on day 15). Dogs in the reversibility segment were bled weekly to monitor ALP, SGPT & SGOT. Hematology, urinalysis, ALP, SGPT & SGOT were determined prior to necropsy. On day 15, ALP was elevated in 6/6, SGPT in 4/6 & SGOT in 5/6 drug-treated dogs, but none in controls.

Slight increases in prothrombin times (but remaining within normal limits) on day 15 in 5/6 sulbactam-treated dogs. Prothrombin times returned to baseline values in all dogs in the reversibility segment.

Serum ALP, SGPT & SGOT were determined at weekly intervals after drug withdrawal. The time elapsed to return to normalcy was as follows: Serum ALP in 6-7 wks; SGOT in 1-6 wks; SGPT requiring 1-7 weeks to return to acceptable levels. The variability of SGOT & SGPT was further evidenced by the fact that 1/4 dogs in the reversibility segment manifested no elevation in these parameters on day 15 (as a direct result of drug treatment) but did show SGPT elevations between days 31 & 59 after liver biopsies performed during this time. Liver biopsy per se did not produce elevation in serum transaminases or alk. phos.

Urinalysis: Unremarkable

Liver Biopsy: All dogs (treated & controls) on Day 16 of dosing. Two treated & one control dog also on days 24, 26 & 102. Liver biopsy materials on days 16, 24 & 26 from control and drug-treated dogs were examined microscopically; there was an apparent hepatocellular glycogenosis in drug-treated dogs (PAS staining). The investigators described the hepatic lesion as follows: "This apparent hepatocellular glycogenosis appears to be comprised of a redistribution of cellular glycogen to a position near the cell membrane at the canalicular and sinusoidal margins of the hepatocyte causing a parentheses-like appearance around the centrally located nucleus. This compartmentalization of the hepatic intracellular glycogen into dense packets located peripherally near the cell membrane constitutes an unusual storage pattern that deviates from normal. The glycogenosis appears equally distributed with no area of the hepatic lobule being more predominantly affected than the another. No other hepatocellular alterations were seen."

The liver from 2/3 drug-treated M necropsied on day 19 revealed the continued presence of the apparent hepatocellular glycogenosis previously diagnosed on day 16. However, the magnitude of the glycogenosis on day 19 appeared substantially reduced (approx 50%) in these dogs as compared to biopsies taken from the same animals 3 days earlier.

On days 113/114 the remaining dogs (1M & 3F drug-treated; 1M & 1F controls) on the reversibility segment were necropsied. None of the drug-treated dogs showed any evidence of hepatocellular glycogenosis. No other hepatocellular alterations were observed.

Conclusive microscopic evidence for the reversal of the hepatic lesion was thus obtained in 1 drug-treated F (Rpt. No. 70204) by biopsy (on day 102), 85 days after the last dose, and in the remaining drug-treated dogs at necropsy (days 113/114), 96/97 days after their last dose of the drug.

The hepatic lesions in all dogs are tabulated below:

Reversibility of Hepatic Glycogenosis
(Drug Withdrawn on Day 17)

Necropsy #/ Animal #	Dose mg/kg/day	Day 16 Biopsy	Day 19 Necropsy	Day 24 26 Biopsy	Day 102 Biopsy	Day 113, 114 Necropsy
A27806/7-32001- M	800	+	+*	N	N	
A27807/7-32009- M	800	+	+*	N	N	
A26816/7-31998- M	800	+		+	+–	-
A28856/7-02038 -F	800	+		+	N	-
A28858/7-02039- F	800	+		+	N	-
A28818/7-02040 - F	800	+		+	-	-
A28817/7-32010 - M	0	-		-	-	-
A28857/7-02050 - F	0	-		-	N	-

+ Hepatic glycogenosis
- Normal hepatic glycogen
N Biopsy not taken
*Necropsied on day 19 after 48 hour fast and two days after drug withdrawal.

<u>Discussion of Results:</u> The investigators stated:

//Liver biopsy after the 16th dose confirmed the presence of an intracellular redistribution of hepatic glycogen identical to that observed previously in the dog after one month of drug treatment (protocol number 77-225-10). On day 15, <u>ALP</u> was elevated in 6/6, SGPT in 4/6 and SGOT in 5/6 CP-45,899-2 treated dogs but not in controls. A causal relationship is therefore implied between the presence of the hepatocellular glycogenosis and serum elevations of these enzymes. Since there was <u>no</u> evidence of focal widely scattered hepatic necrosis, transaminase elevations are probably a result of altered membrane permeability brought about either by the very high serum levels of drug achieved ($\sim$2200 µg/ml or $\sim$9.4 µM/ml) and/or by the intracellular redistribution of hepatic glycogen to a peripheral position near the cell membrane. ALP elevations are probably hepatic in origin since there was a concomitant increase in serum transaminase levels. Since ALP is a microsomal membrane-bound enzyme which is incapable of "leaking" during altered hepatocellular permeability, increased serum levels are probably related to increased intracanalicular hydrostatic pressure, a factor known to induce alkaline phosphatase production and serum release by a yet unknown mechanism (1).

Although the reversibility of the serum enzyme elevations may have been complicated somewhat by surgical procedures, ALP seems to exhibit the most consistent pattern, requiring 6 to 7 weeks to return to normal levels. Transaminase elevations and their reversibility appear more variable; some dogs demonstrated no elevations on day 15, others with elevations returned to normal after only 1 week; still others did not return to normal until 6 to 7 weeks had elapsed since the last dose of drug. Since the duration of serum transaminase elevation is dependent upon its persistent leakage from hepatocytes, very high serum levels of CP-45,899-2 would not seem to be the sole cause of apparent membrane permeability alterations. However, if the redistribution of intracellular hepatic glycogen is responsible for ALP elevations through increases in intracanalicular hydrostatic pressure, the consistency with which this parameter returns to baseline values may reflect, to some degree, reversibility of the hepatic lesion.

The reduction in the magnitude of the hepatic glycogenosis observed in the two male dogs necropsied on day 19 after a 48 hour fast was probably produced by the removal of residual normal glycogen that is still present in the dog after only an overnight fast and does not indicate rapid reversibility of the hepatic lesion. Conclusive evidence for the reversibility of the lesion was obtained on day 102 (85 days after the last dose of drug) where biopsies revealed that the liver of one female dog (702040) was essentially normal and the liver of the other dog (731998, male) had only a mild hepatic glycogenosis. At necropsy, (96-97 days after the last dose of drug) all livers of the remaining dogs had returned to normal.

Conclusions

CP-2 at 800 mpk/day for 17 consec. days was very well tolerated. The drug did induce a reversible hepatocellular glycogenosis (PAS +) comprised of a redistribution of intracellular glycogen into dense packets located peripherally in the hepatocytes. Associated enzyme elevations of alk. phos., SGOT & SGPT were also reversible. No other hepatic lesions.

The investigators conclude, "The compartmentalization of hepatic intracellular glycogen is an unusual finding and constitutes a storage pattern that deviates from the normal diffuse intrahepatocellular storage of glycogen. However, the lesion is fully reversible and the mechanism by which it occurs is currently under investigation."

4. Seven-day IV & Oral Range Finding Study in Male Rats: [Rpt. No. 77-225-02]

Material Tested: CP-2

Animals: SD rats from Charles River; M only; 5 rats/gp

Dosage Levels: CP-2 @ 800, 600 & 400 mpk/day orally and @ 600 & 400 mpk IV for 7 consec. days.

Results: No clinical signs of compound-induced toxicity were reported. Gross & histopathology of major organs reportedly showed no alterations.

5. One-month IV Study in Rats with CP-2 Singly & in Combo with Ampicillin: [Rpt. No. 77-225-03]

Material Tested: CP-2 alone or in combo with ampicillin Na

Animals: SD (CR) rats; total of 50 M + 50 F

Groups:

	Dose (mpk/day)		
	CP-45,899-2		Polycillin-N
A	400 (IV)		0
B	200 (IV)		0
D	200 (IV)	+	200 (IV)
E	200 (IV)	+	200 (oral)
C	Controls (saline)		0

Rats were dosed once daily for 36 days.

Results: Two rats died; 1 HD F on day 6 of accidental asphyxiation and one combo (Gp. D) M was sac'd due to severe malocclusion (teeth?) causing malnutrition. Occasional soft stool & diarrhea occurred in the HD & LD gps during the first week. Decreases in food intake and slowing in rate of body wt gain were observed initially in treated gps, but on termination the differences were smaller.

Ophthalmic Exam: Performed using a hand-held direct ophthalmoscope; done at pre-test and on day 36. No drug-induced ocular changes were noted.

Clin. Chem.: Stat. sig. increases in SGOT & LDH on day 37 in all M drug gps and SGOT in F gps receiving CP-2 IV & ampicillin PO (Gp. E). Hematology and urinalysis were unremarkable.

Pathology: "There were no gross or histopathologic lesions that could be attributed to the administration of CP-2 alone or in combination with ampicillin."

Note: No mention of glycogenosis either in the tables or in the text. Marginal increases (stat. sig) in rel. liver wt were observed in all M treated groups.

6. One-month IV Study in Rats with CP-2 Alone or in Combo with Penicillin G: [Rpt. No. 77-225-11]

Material Tested: CP-2 (Na penicillinate sulfone)

Animals: SD (CR) rats; 10/sex/gp

Groups & Treatment

CP-2	800 mpk in terms of CP
"	400 " " " " "
"/Pen. G	200/100
Controls	0 (Saline)

Rats were injected IV once daily for 30 consec. days.

Results: Two rats from the combo gp died (1 M on day 7 of suffocation; 1 F after dosing, showing convulsions and bleeding from the mouth).

Injection site trauma (6 HD & 2 LD) necessitated infrequent SC injection of CP-2 alone in 6/40 rats (see Table I of report). However, inj. site trauma in the combo group (20/20) required SC admin. much more frequently. [Note: The cause of this discrepancy among groups has not been explained in the report.

Minor changes occurred in body wt gain. The primary effect of the drug was a dose-dependent increase in PAS-staining characteristics of liver sections - the so called "glycogenosis" - alteration of cellular glycogen distribution suggestive of increased glycogen storage. This was dose- & sex-related. In F, the response was slight at the MD and absent at the LD in the combo gp with penicillin G. M showed a slight effect in the combo gp. Increased abs. & rel. liver wts occurred in the HD M & F and the MD M.

Clin. Chem: Elevated serum K values were not consistent between M & F and lacked dose-response relationship. SGPT values had decreased in M & F at the HD. Urinalyses were reportedly unremarkable.

Injection site reactions were within the range of tissue alterations with the dosing procedures.

Subcutaneous Route

7. One-month SC Study in Beagle Dogs with CP-2 Followed by Drug Withdrawal for Reversibility: [Rpt. No. 78-225-12]

Material Tested: CP-2

Animals: Beagles; total of 9 M + 9 F; 3/sex/gp

Methods: CP-2 at doses eqiv. to CP free acid 0, 100 & 200 mpk b.i.d. (total daily dose: 200 & 400 mpk/day) was injected SC for 35 consec. days.

At the end of 35 days, 3/sex LD, 1/sex HD & 1/sex control dogs were sac'd. The remaining 2/sex HD dogs and controls were withdrawn and placed on a restricted diet (reduced intake of standard diet not to exceed 20% reduction in body wt). This reversibility group was sac'd on days 106-109.

Results: No mortality; loose stools in 5/6 HD, 4/6 LD & 5/6 controls dogs.

Clin. Chem.: Elevated serum alk. phos. (ALP) in 4/6 HD dogs after 15 days, and in all HD dogs at day 35. ALP returned to pre-test levels in 3/4 HD dogs within 9-28 days after cessation of treatment. Very slight elevation in SGOT level occurred in 3/6 HD dogs after 35 days of dosing.

Glucose Response to Glucagon: Forty-eight hrs after treatment withdrawal, and again on 3 subsequent occasions, 1/sex from treated & control gps were evaluated. Glucagon was admin. IV at 1 ug/kg; glucose levels were measured for 30 min. A second glucagon dose of 4 ug/kg was then admin. and glucose levels were again monitored for an addl. 30 min. (no eval. during dosing period).

In general, on days 44 & 51, the glucose response to glucagon in treated dogs showed a tendency to return to the value in controls. Although the response of the treated animals only reached approx. 75% of controls following the first challenge of 1 ug/kg glucagon, following the 2nd challenge (4 ug/kg) they seemed to be restored to 100% control response. On day 65, the glucose response to the 2nd challenge (4 ug/kg) was also back to control values, although the response to the initial challenge (1 ug/kg) remained low.

Hematology & Urinalysis: Stat. sig. increase in prothrombin time in HD M on day 35. However, all values were within normal limits. Urinalyses for all dogs were unremarkable.

Gross & Histopathology: [Note: Glucogenesis, its histological grading system and incidence, were provided in detail in this study.]

The grading system involved two factors (a) the no. of cells affected; (b) the degree of redistribution of glycogen. The former was invoked at grades 1 & 2 where not all cells were altered, while the latter reflected progressively increasing amounts of glycogen located in the periphery of the cell rather than having its usual diffuse intracellular distribution.

Hepatocellular glycogenosis incidences were: HD (400 mpk/day) - both dogs killed on day 35; LD (200 mpk/day) - 1/3 M & 3/3 F on day 35. On an arbitrary scale of 1-4, HD dogs had changes graded as 4+ in M and 3+ in F. In the LD gp, 1 M was graded 2+ and 3 as 1+. The remaining 2 F were essentially normal.

In the reversibility part of the study, on day of terminal sacrifice, both HD M had returned to normal but 1 HD F still had grade 1 (on day 66) and the other was normal; controls were normal.

The wt changes and spermatogenesis seemed to be within normal limits and changes, if any, were due to individual variations.

8. Special 10-Wk SC Study in Rats With CP-2 (14-29 Daily Doses Followed by Drug Withdrawal): [Rpt. No. 78-225-16]

Study Dates: 6/26/78 to 9/6/78

Objective: Previous expts with CP-2 in both dogs and rats showed a dose-related hepatic glycogenosis (PAS+). Transaminase & alk. phos. elevations occurred in time- & dose-related fashion in the dog, but not in the rat, and were believed to be associated with hepatic glycogenosis. Additionally, neither ampicillin Na nor penicillin G K co-administered with CP-2 appeared to potentiate these effects in either species.

This study was designed to evaluate the time-course of onset and reversibility of the apparent hepatic glycogenosis induced by CP-2 in rats.

Material Tested: CP-2; each vial eq. to 0.5 g CP (free acid)

Animals: Total of 68/sex Sprague-Dawley (CR) rats; 17/sex/group

Drug Treatment

Compound	Dose (mpk)*	Conc'n (mg/ml)*	Vol (ml/100 g body wt)
CP-2	400	250	0.16
"	200	250	0.08
"	100	250	0.04
Controls	0	0.9% NaCl	0.16

* mg of CP as free acid

Rats were injected SC once daily. The number of doses/group varied from 14-29, according to experimental design (see Table, page 13). The no. of doses depended on histo confirmation of glycogenosis. Cessation of dosing for reversibility for an entire group was instituted when positive diagnoses of glycogenosis were made, with the exception of the LD gp. Dosing was contd. for 1 week in the LD gp after positive diagnosis for glycogenosis was made.

Gross & Histopathology: Although all the usual organ tissues were taken for histology, only the results of liver changes (glycogenosis) were included in the report. Hepatic glycogenosis was graded on a scale from +1 to +4 (+1 with least and +4 with most PAS-positive material).

Results: Only those pertaining to hepatic glycogenosis are described.

HD (400 mpk/day)

- occurred in M & F on day 15 (after 14 doses); dosing discontinued after the 15th dose;
- greater in M than in F;
- in reversibility expt, a gradual decrease in degree in both M & F with time, until F appeared normal after 21 days and M after 49 days.

injection site in all drug-treated dogs, which later spread from the inj. site over the entire dorsal area. [Histo. mild to slight fibrosis, chronic cellulitis & hemorrhage in the subcutis of few dogs - local reaction]

Vital signs, EKGs tracings & indirect systolic BP showed normal variations. No treatment-related ocular alterations (hand-held ophthalmoscopy pretest and on days 92 & 183).

Clin. Pathology: Serum chem., hematology & urinalysis were performed twice on all animals pre-test and on days 15, 29, 43, 64, 85, 113, 141, 162 & 183.

Serum Chemistry: Statistical summary of serum chemistry is tabulated (please see Table II, NDA Vol 1.22(d), pp. 1350-1357).

With the exception of apparent slight dec. in fasting glucose (treated & control gps), a markedly elevated ALP in 1/4 control F and isolated slightly elevated SGOT values (combo gp, 1 M & 1 F; LD, 1 M & 1 F; HD, 1 F; controls, 1 F), all individual values showed normal variability. The low blood glucose values were suspected to be due to time delay in refrigeration of samples. Thus, on day 183 (terminal) most, but not all, blood glucose values were higher than those observed on day 162. However, at that time several controls still showed slightly low blood glucose values equivalent to those observed during the study period in both treated and controls. According to the investigators, these changes were not drug-related.

SGOT: No statistical differences in M or F in any gp.

SGPT: No stat. diff. in F in any gp; lower in 60 mpk M on day 183, but slightly higher in HD M on day 162 - biol. insig.

ALP: No stat. diff. in M or F of any gp

Hematology & Urinalysis: Normal variations; no drug-related effects.

Liver Total Glucose & Glycogen Analysis

Total glucose (glycogen + free glucose) and perchloric acid (PCA)-insoluble glycogen were analyzed in livers of all dogs. All dogs were fasted for 24 hrs prior to necropsy. The value for total liver glucose includes all forms of glucose within the tissue (free glucose, PCA-soluble glycogen & PCA-insoluble glycogens).

The investigators state, "No stat. sig. change in total liver glucose was associated with admin. of any dose of CP, in either M or F dogs. There was however, an increase in the amount of PCA-insoluble glycogen, which was dose-related and stat. sig. except at 20 mpk/day of CP in M. A converse decrease in PCA-soluble liver glycogen occurred at doses of 120 and 60 mpk/day, as determined in qualitative expts."

Gross & Histopathology

No differences in wts of liver, kidney and testis. [Histo: testis not listed; presumably normal.]

Drug-induced hepatocellular glycogenosis not exceeding 1+ (scale of 1-4) occurred in 4/4 M & 3/4 F at 120 mpk and in 3/4 M & 3/4 F at 60 mpk. No evidence of glycogenosis was observed in any animal in either the LD (20 mpk) or combo (20/20mpk) gp.

Discussion & Conclusions Dose-related stat. sig. increase was noted (except in 20 mpk M) in PCA-insoluble glycogen, with a converse decrease in PCA-soluble liver glycogen at the higher doses. Histo. evidence of marginal glycogenosis was observed at the HD (120 mpk) & MD (60 mpk), but in neither the LD (20 mpk) or combination (20/20 mpk) groups. The investigators state," The greater sensitivity of the biochemical method may have been due to the high levels of liver glycogen remaining in the dogs following the 24-hour ante-mortem fast, obscuring any marginal morphological changes. (Underlining mine.) Therefore, CP when given alone or in combination with ampicillin at the proposed clinical level to beagle dogs for a period of 6 months produced no clinical or morphological evidence of toxicity and only a slight accumulation of PCA-insoluble glycogen in liver."

They further add:

"Histochemical studies have shown this material to be completely digestible by malt diastase, an enzyme known to hydrolyze liver glycogen. Biochemical studies have demonstrated an excess amount of acid-insoluble liver glycogen which has been found to be a sensitive biochemical marker for the accumulation of the histologically identifiable PAS-positive material in drug-treated animals. In previous experiments, the two phenomena were closely correlated over a variety of dose-response, progression and regression situations. Other work has shown that the acid-insolubility of the glycogen from livers of drug-treated animals was due to its association with intracellular protein(s). Additionally, no other carbohydrate containing material other than glycogen was found in abnormal amounts in livers of treated animals. All available evidence suggests that the glycogen molecule per se is structurally normal.

The formation of this material in the liver is apparently a result of a direct drug action, develops in a dose- and time-dependent fashion, and is reversible upon drug withdrawal. It is not similar to the known glycogen storage diseases.

Although intended for short-term antibacterial therapy in man (ca. two weeks), the effects of parenterally administered CP-45,899-2 alone or in combination with ampicillin were examined in beagle dogs under chronic conditions (six months), at doses projected to be 1, 3, and 6 times human use levels and are described in this report. Additionally, at the termination of this study, biochemical analysis of glucose and glycogen in liver samples from each animal was conducted in an attempt to correlate these data with histopathologic observations."

10. Six-month SC Study in Rats with CP-2 Alone or in Combination with Ampicillin: (Rpt. No. 78-225-18)

Study Dates: 7/16/78 to 01/26/79

Material Tested: CP-2; Lot No. ED-V-034-38; 25 mg/ml conc'n of sol'n

Animals: Sprague-Dawley (Charles River) rats; total of 50 M + 50 F; 10/sex/gp.

Drug Treatment

Compound	Dose (mpk)*
CP-2	120
"	60
"	20
" + Ampicillin	20 + 20

* mpk of CP 45,899 free acid

The rats were injected SC once daily for 187-191 consec. days.

Results

Clin. Observations: No observable adverse effects. No dose-related changes in body wt. & food intake. No treatment-related ocular changes.

Clin. Pathology

Markedly elevated BUN in 1/9 LD F; SGPT elevations in 3/10 HD M, 1/10 HD F, 4/10 MD M, 3/10 combo F, 3/10 LD M, 3/10 LD F, 2/10 control M & 4/10 control F. Additionally, 2/10 combo F & 1/10 LD M had marginal increases in SGOT activity. However, all mean values were within normal limits and were not sig. different from controls.

Transient sporadic WBC counts greater than 30 x 10^3 in both treated and controls; otherwise hematology unremarkable. Except for one LD F with alk. pH on and after day 57, consistent protienuria (+1) on and after day 29, as well as varying degrees of hematuria throughout the study. All other urinalyses were unremarkable.

Gross & Histopathology

Hepatocellular glycogen accumulation, glycogenosis on scale 1+ to 4+:

HD (120 mpk/day): Males (see Table VII): 2+ in 6/10 to 1+ in 4/10. These rats also had slightly increased liver wts. Females: 1+ in 6/10; the remaining 4/10 had normal livers.

MD (60 mpk/day): Males: 1+ in 6/10; Females: none (0/10)

LD (20 mpk/day) & Combo Group (20/20 mpk/day): None reported.

Other Lesions: Subcutaneous chronic inflammatory changes (local reaction of drug).

Liver Total Glucose & Glycogen Analysis: (4 rats/group) Dose-response increases in fasting livers of total glucose and PCA-insoluble glycogen were observed in M rats. The increases in both substances were stat. sig. in the MD and HD groups. In the liver of F rats there was no stat. sig. increase in either total glucose or PCA-insoluble glycogen at any dose, nor was a trend toward elevated values apparent, even at HD (120 mpk/day).

In parallel qualitative expts. there was no marked drug-related change in liver levels of either PCA-soluble glycogen or free glucose, in M or F rats, at any dose of CP.

Intramuscular Route

11. IM Irritation Study in Albino Rabbits with Lypholized CP-2 IM/IV: [Rpt. No. 77-225-07]

The local tissue effects of dose volumes of 0.5, 1.0 & 2.0 ml of a 250 mg/ml CP-2 sol'n were evaluated at 3 & 7 days after single IM injection; similar injection with Na ampicillin (Polycillin-N^{R}) served as comparative controls.

The lesions produced by CP-2 sol'n, ampicillin or water were similar histologically. It was concluded that CP-2 was not more irritating than Polycillin^{R}.

12. IM Irritation Study in Albino Rabbits with CP-2 IM/IV Reconstituted with 2% Lidocaine: [Rpt. No. 78-225-14]

Methodology: Same as in the previous study (vide supra) except that the material also contained 2% lidocaine. Histologically, the lesions produced by either CP-2 or water were similar and characterized by interstitial proliferation of fibroblastic cells, coagulation necrosis, hemorrhage, occasional mineralization of the muscle fibers, and inflammatory cell infiltration at the periphery of the lesion. These lesions were related to the volume injected rather than to an irritating effect of the respective test sol'n.

Oral Route: (Not the proposed route of admin.)

13. 5-Day (4-dose) Oral Range Finding Studies in Dogs: [Rpt. No. 77-225-01]

Animals: Beagles; 1/sex/dose

Treatment: CP @ 400, 400 & 800 mpk/day; controls - empty gelatin capsule. Dogs dosed once daily for 4 consec. days, observed 2x/day and necropsied on day 8.

Results: No mortality. No signs of toxicity. Serum chem., hematology, and urinalysis were negative. No drug-related gross or histo. findings.

Results

No clinical signs in drug-treated or controls animals.

Pregnancy rates of 90, 80, 90, 95 & 85% in controls, LD, MD, HD and combo gps, respectively; 11 matings (1 HD, 2 MD, 4 LD, 2 combo gp and 2 control animals) did not result in pregnancy.

At day-14 (mid-gestation) & day 21 of lactation, no drug-related effects on reprod. parameters, survival and body wts of pups.

#2. Segment II Teratology Study in Mice (IM Route): [Rpt. No. 78-0951 [Conducted by Laboratoires PFIZER, France.]

Material Tested: CP-2

Animals: ICR Swiss mice [from Charles River Labs. (France)]; 25 F/gp

Groups & Treatment: Controls, CP (free acid) @ 200, 400 & 800 mpk/day; administered IM once daily from gestation days 6-13 (sperm positive = day 0). On day 17 p.c. mice were necropsied and evaluated for various terata parameters, including (a) staining of uteri (Salewski method), (b) staining skeleton by alizarin red, and (c) sectioning fetuses (Wilson technique).

Results

Maternal Toxicity: One HD pregnant F died (accident); no drug related effects on body wt gains, or reproductive parameters.

Fetal Development: No drug-related effect on fetal growth.

Fetal Abnormalties

External: One LD (200 mpk) fetus had deformed left hind paw.

Visceral: One control fetus showed bilateral hydronephrosis & one LD (200 mpk) fetus had cleft palate.

Skeletal: One MD (400 mpk) fetus showed absence of palatine bone. The percentage of delays in ossification was noted in all groups including controls and drug-treated groups, and was concluded to be not drug-related.

#3. Segment II (Teratology) Study in Rats (IM route): [Rpt. No. 78-096] [Conducted by Pfizer Labs, France]

Material Tested: CP-2

Animals: Charles River SD rats; 20 F/gp

Groups & Dose Levels: Controls, CP (free acid) @ 200, 400 & 800 mpk/day, injected IM once daily from gestation days 6-15 (vag. plug = Day 0). On day 20 p.c. all rats were killed and evaluated for various terata.

Results

Maternal Toxicity: No mortality. Slight growth inhibition (stat. sig.) at 400 & 800 mpk. No sig. differences in reproductive parameters.

Fetal Development

Fetal Wts: Stat. sig. were: 200 mpk M & F were slightly less than controls; in 400 mpk M & F, wts were slightly higher than the controls.

Abnormalities

External: one HD (800 mpk) fetus showed "kinky tail" syndrome with twisted tail, protruding tongue, syndactylia of both hind paws and tetradactylia of forepaws.

Visceral & Skeletal: None ascribed to drug treatment.

#4. Segment II (Teratology) in Rabbits (IV Route): [Rpt. dated Nov. 1984; conducted by Nagoya Pharmacology Laboratory, Pfizer Taito Co., Ltd., Japan.]

Material Tested: CP-2 vial containing equivalent to 0.625 g free acid was reconstituted with 2.0 ml of sterile water. This sol'n was then diluted with normal saline to obtain conc'n. of 100 mg/ml.

Animals: Japanese white rabbits; total of 58 F; 14-15 preg. rabbits/gp

Groups & Procedure: Saline controls, CP (free acid) @ 50, 100 & 250 mpk/day; injected IV once daily from gestation days 6-18 (copulation day = Day 0). All rabbits were killed on day 29 of gestation. All live fetuses were weighed and crown-rump length measured; 2/3 fetuses of each litter were necropsied and examined for sex determination and internal abnormalities, then stained (alizarin red) and examined for skeletal malformation and degree of ossification. The remaining 1/3 fetuses were examined for visceral malformations by sectioning technique.

Results

Maternal Toxicity: No toxic signs; no abortion; no mortality. Mean body wt gains at the HD (250 mpk) were slightly but not significantly less than in controls; other groups not affected. (Note: In their prelim study, body wt loss was noted at 500 mpk dose). The no. of corpora lutea and implants were comparable in treated & controls. Mean placental wt at the HD (250 mpk) were sig. less than in controls; other gps were comparable.

Fetal Development: Mean fetal wt at 250 mpk was sig. lower than in controls; other gps not affected. Fetal crown-rump tail lengths were comparable in treated and control gps.

Fetal Abnormalities: No external, visceral or skeletal malformations were reportedly observed in the control or treated groups. The incidence of skeletal variations (e.g., extra 13th rib) in the treated groups (33%-39%) was higher than in the controls (20%), but this variation was, according to the investigators, within the normal range.

Conclusion: CP-2 at doses up to 100 mpk/day was devoid of maternal toxicity or teratogenicity in rabbits.

#5. Perinatal & Postnatal (Segment III) Study in Rats (IM): Rpt. No. 80-010 dated 3/10/81; conducted by Pfizer Lab, France.]

Material Tested: CP-2

Animals: Charles River (France) SD rats; 20 F/gp.

Dose Groups & Procedure: Controls, CP (free acid) @ 200, 400 & 800 mpk/day, injected IM once daily from day 15 post-coital thru parturition and up to day 20 post-partum (day preceding weaning). Treated dams killed at weaning; 5 pups/sex/dose level sac'd at weaning.

Results: The treatment induced a slight growth inhibition of the dams at the end of gestation, but did not affect pregnancy, fertility or lactation. Growth of pups born to dosed mothers was normal; their survival was not affected. The postnatal development of pups and the visual & hearing functions were normal. In behavior, only a depression of the exploratory activity (rearing) of the offspring, possibly related to their slightly lower mean weights, was noted. No drug-related anomaly was reportedly found at necropsy of the offspring.

Genetic Toxicology

Material Tested: CP-2 (Lot No. 9571-102-AH)

1. Ames Plate Assay: Point mutation assays in histidine auxotrophs of *S. typhimurium* at levels ranging from 10.0 to 0.0005 mg/plate did not produce increased reversion frequency, and gave negative results with metabolic activation. Urine collected from mice dosed IP with 1000, 500 & 50 mpk of CP-2 did not show the presence of mutagenic metabolites when tested on five tester strains.

2. Forward Mutation Assay: Using *E. coli* 343/113, no sig. mutagenic activity was reported at the galactose locus when CP-2 was applied at levels ranging from 50.0 to 0.02 mg/ml.

3. Assay Utilizing DNA Repair-deficient *E. coli* (Pol A^-): Did not produce a significant response when tested at levels 1.0 to 0.01 mg/disc.

4. Assay Using Yeast: An assay using *S. cerevisiae* strains D-3 & D-4, CP-2 at levels of 20.0 to 0.2 mg/ml did not show a dose-related increase in mitotic recombination or mitotic gene conversion.

5. <u>Cytogenetic Studies: In vivo</u>: Mice rec'd an acute IP dose of 1000 mpk and a subacute dose of 500 mpk/day for 5 days. Results showed no increase in abnormal cells over historical controls. In vitro results in human lymphocytes using culture medium levels of 1000, 100 & 10 ug/ml of CP-2 were negative.

Special Biochemical Study

<u>Characterization of Liver Glycogen Associated with CP Administration: [NDA Vol. 1.1, pp. 65-119]</u>

This study was conducted by Pfizer's Pharmacology Research Dept. to investigate the biochemical nature of the glycogen-like, PAS-positive material, to explore possible mechanisms & pre-conditions for its formation, and to evaluate physiological & clinical consequences of its presence in the liver.

The "Discussion" portion of the report (pp. 46-51) addresses several issues: (1) the nature of the PAS-positive deposits, including their distribution within the liver; (2) proposed mechanism for formation and removal of the glycogen deposits; (3) clinical significance and consequences for carbohydrate metabolism.

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Conclusion: The investigators state, "The weight of evidence from this study indicates that sequestration of protein-bound glycogen is the only significant effect of CP on glucose homeostasis. This effect can account for essentially all the known characteristics of the deposited material. Furthermore, the dosing-feeding schedule adopted for safety trials may have inadvertantly produced the maximum possible amount of hepatic glycogen deposition. Finally, there is little likelihood that CP will alter carbohydrate metabolism in any significant way in either diabetic or non-diabetic patients, because of the absence of direct drug effects on the major pathways of carbohydrate metabolic flux."

Absorption, Distribution, Metabolism & Excretion

The following 3 studies in animals were submitted (NDA Vol. 1.3):

1. Serum Conc'n in Rats Following High Doses of Sulbactam: [Study No. 16]

The objective was to determine serum levels following high doses, e.g., used in toxicology studies.

Methods: Rats were given 200 mpk Sulbactam IV (2 rats/time point), 120 mpk SC (3 rats/time point), or 400 mpk IM (3/time point). Additionally, urine was collected for 24 hrs from rats injected SC at 400 & 800 mpk sulbactam for 14 days.

Results

Comparison of dose regimen following admin. of sulbactam:

Dose (mpk)	Route	Mean AUC (ug hr/ml)	C_{max} (ug/ml)
200	IV	110	202
120	SC	77	83
400	IM	381	538

AUC appeared to be related to dose regimen, C_{max} (peak conc'n) varied substantially. The urinary recoveries (25-45 of dose) following SC admin. of the HD were similar to those (31%) following lower parenteral doses (10-25 mpk).

2. Kinetics of Parenteral Sulbactam in Beagle Dogs: [Study No. 17]

Methods: Three dogs were admin. sulbactam at doses of 100, 200, 400 & 800 mpk, IV. Sets of 2 dogs were given IM or SC doses of 400 mpk. Another set of 2 dogs was given 2 x 200 mpk SC doses every 3 hrs. Serum from the jugular vein (contralateral to the site of IV injection) was assayed.

Results: The half-life of sulbactam in the dog was approx. 50 min. The fit of the data to a 2-compartment model was excellent with goodness of fit (r^2) greater than 0.990 for all curves. The 800 mpk data were interpreted as a 1-compartment model, since the 2-compartment model did not provide a significant improvement in the fit to the curve.

Interpretation: Serum conc'n at each time point and AUC's following IV doses were proportional to dose. The apparent volume of distribution for the central compartment, V_c (blood and rapidly equilibrating tissues), was approx. 210 ml/kg. The whole-body apparent vol. of distribution, V_b, was approx. 340 ml/kg. Between 1/2 & 2/3 of the drug was in the central compartment in the post-distribution phase.

Although SC & IM doses produced lower peak conc'n, the total exposure of the animals to drug (AUC's) was similar to that following equal IV doses.

Summary of IV Kinetics of Sulbactam in Beagle Dogs: (Based on mean serum conc'ns of 3 dogs/dose level.)

Parameter	Mean Parameter Value Dose (mg/kg) 100	200	400	800*
β	0.887	0.818	0.880	0.880
r^2	0.991	0.998	0.996	0.992
AUC+ (μg hr/ml)	348	804	1206	2602
k_{12} (hr^{-1})	0.547	6.69	1.28	
k_{21} (hr^{-1})	1.78	8.64	3.48	*
k_{10} (hr^{-1})	1.43	1.52	1.31	
V_c (ml/kg)	201	164	253	
V_b (ml/kg)	324	304	377	349
f_c	0.62	0.54	0.67	*

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*1 compartment

+0-∞ hours.

3. Penetration of Sulbactam into Rat Fetuses: [Study No. 19]

Methods: Pregnant rats (2/time point) were injected IM (thigh) with sulbactam Na @ 800 mpk. The dams were killed @ 15 min., 1 hr & 3 hrs post-dosing, and 4 fetuses from each dam were sampled.

Results: The conc'n in the maternal blood and in the fetuses decreased rapidly between 0.25 & 3 hrs. The conc'n was above 200 ug/g in all fetuses at 0.25 & 1 hr. At 3 hrs, fetal conc'ns were greater than those in maternal serum.

Interpretation: Sulbactam crosses the placenta rapidly, and high conc'ns of the drug were found in the fetuses. (Note: Tissue distribution in the fetus was not reported.)

SUMMARY & COMMENTS

1. Sulbactam is a beta-lactamase inhibitor, being developed by Pfizer Labs for use with beta-lactam antibiotics.

2. Sulbactam is a penicillin sulphone. It structurally resembles clavulanic acid in that the C-6 acylamino side-chain is missing, and there are close functional parallels with clavulanate in terms of its interaction with the target enzyme. It is a potent competitive inhibitor of the homogeneous RTEM beta-lactamase. Although bound tightly to the enzyme, it is quite resistant to enzymatic hydrolysis. Unlike clavulanate, there is no evidence for the formation of a transient complex between sulbactam and the enzyme, and the sulphone is only a lethargic inactivator. The half-time for irreversible inactivation of beta-lactamase by sulbactam is 44 min. with an inactivating event occurring approximately every 4500 turnovers. This is much less effective than clavulanic acid, the inactivation half-time of which is 8 min., with 150 turnovers before inactivation. [NDA Vol. 1.5, pp. 1306-07]

3. Acute toxicity of a single IV dose of either sulbactam or the antibiotic combination is quite low (more or less similar to other beta-lactam antibiotics).

4. The most striking effect of repeated administration of sulbactam (alone or in combination) was an unusual drug-induced hepatic lesion, and an associated elevation of liver enzymes in the serum. This lesion, referred to as "glycogenosis", occurs in both rats and dogs. It is described histologically as increased PAS-positive deposits (glycogen) occurring in dense aggregates located peripherally within the cell. The available evidence suggests that this glycogen is essentially of normal structure, but is acid insoluble and is found in close association with cellular protein.

   Although the drug-related glycogen was inert to glycogenolytic stimuli (e.g., fasting, glucagon challenge), the lesion was reversible with time, as were the serum enzymes. It has been hypothesized that sulbactam may have an effect on an enzyme of glycogen metabolism (e.g., glycogen synthase) similar to the desired effect on beta-lactamases.

   The significance of this phenomenon with regard to humans is not known. If a similar phenomenon can occur in man, the fact that it is reversible could be considered a mitigating factor.

5. It is recommended that a summary description of the rat & dog liver findings be included in the labeling.

S.R. Joshi, D.V.M., Ph.D.

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SUMMARY & EVALUATION

2-3. SUMMARY AND EVALUATION

[illegible]. SCIENTIFIC RATIONALE AND PURPOSE

3. HIGHLIGHTS OF CLINICAL STUDIES

After careful profiling of the antibacterial spectrum of sulbactam/ampicillin, a comprehensive program was carried out to evaluate its clinical efficacy and safety.

To date, sulbactam/ampicillin has been used in various clinical settings to treat 1764 patients. This submission is an analysis of the 1,105 evaluable patients for whom case record forms were available at the time of data cut-off.

a. Rationale and Organization of Clinical Program

Sulbactam/ampicillin was tested clinically in both the U.S. and Europe. The purposes of the clinical evaluation include the following:

1) To evaluate the efficacy of the sulbactam/ampicillin combination for the treatment of serious bacterial infections of a variety of organ systems.

2) To evaluate the efficacy of the drug against an expanded spectrum of pathogens such as beta-lactamase producing strains of *H. influenzae*, *Klebs. pneumoniae*, *Staph. aureus*, *Staph. epidermidis*, *E. coli*, *Branham. catarrhalis*, *Prot.* spp., *Enterobacter* spp., *Morganella morganii*, *Acin. calcoaceticus* var. *anitratus* and anaerobic *Bacteroides* spp. and *Peptococcus* spp. In addition, mixed infections with a polymicrobic flora containing ampicillin susceptible micro-organisms are also amenable to sulbactam/ampicillin treatment due to its ampicilli[illegible].

3) To evaluate the safety of the drug.

Data reported in this submission were obtained in open and comparative clinical studies of sulbactam/ampicillin and were conducted by a total of 75 investigators.

b. Indications Evaluated

A total of 744 patients reported in this submission were treated in 15 controlled clinical trials, which were well monitored, and followed well defined protocols. The total of 744 includes 404 patients who received sulbactam/ampicillin and 340 who received comparative antimicrobials.

The indications evaluated included many types of infections including:

Upper and lower respiratory tract infections
Skin and skin structure infections
Urinary tract infections
Intra-abdominal infections
Gynecological infections
Bacterial septicemia
Bone and joint infections
CNS infections

The efficacy of sulbactam/ampicillin in a prophylactic/perioperative setting was also evaluated in 8 studies which included 579 sulbactam/ampicillin and 768 control patients.

c. Qualifications for Efficacy Evaluations

All of the available case record forms were carefully analyzed and evaluated for efficacy and safety. The patients were classified into efficacy assessment categories as follows:

Bacteriological response

Only those patients from whom pre-therapy (i.e., baseline) pathogens were isolated were considered fully evaluable. The bacteriological efficacy responses used in the analysis were categorized as follows:

1) Eradication - elimination of initial principal baseline pathogen(s) or no culture obtainable at the end of therapy (i.e., no specimen obtainable).

2) Eradication with superinfection - elimination of initial pathogen(s) at the end of treatment but with emergence of different pathogenic organism(s) during or at the end of treatment.

3) Eradication with reinfection - elimination of initial pathogen(s) at the end of treatment but with later appearance of different pathogen(s).

4) Eradication with recurrence - elimination of initial pathogen(s) at the end of treatment but later re-emergence of the initial pathogen(s).

5) Persistence - initial pathogen(s) cultured at the end of treatment.

Clinical response

1) Cure - Defervescence and disappearance of all presenting signs and symptoms at the end of therapy.

2) Improvement * - Disappearance of some presenting signs and symptoms or reduction in number and severity of most signs and symptoms at end of therapy.

3) Failure - No appreciable change in number or severity of presenting signs and symptoms at end of therapy.

* In some of the studies "Improvement" was divided into sub-categories designated "Marked," "Moderate" or "Slight"; however in this submission "Slight" improvement was classified as an unsatisfactory response.

Overall response

Patients who had both evaluable bacteriological [illegible] responses, were assigned an overall response categorized as either Satisfactory (i.e., cure) or Unsatisfactory (i.e., failure), based on the last visit at end of therapy. An overall Satisfactory response required a bacteriological response of eradication, eradication with superinfection or eradication with reinfection together with a clinical response of cure or improvement. ("Slight" improvement was classed with an unsatisfactory overall response). An overall Unsatisfactory response was defined as bacteriological persistence during or at the end of therapy and/or clinical failure (or only slight improvement).

d. Overview of Clinical Experience

1) Of the 2,872 patients entered into the clinical program, 1,764 were treated with sulbactam/ampicillin in comparative and non-comparative studies. Of the sulbactam/ampicillin treated patients, 1,105 (640 in therapeutic studies) qualified for evaluation of drug efficacy. An overall SATISFACTORY response for sulbactam/ampicillin therapy was achieved in 88.3% (565/640) [illegible] (excludes prophylactic/perioperative status).

   A total of 1,108 patients received one or more comparative agents. In this comparative group, 801 (200 in therapeutic studies) patients could be evaluated for efficacy. The overall SATISFACTORY response for the patients who received a comparative agent was comparable to that for sulbactam/ampicillin 90.0% (108/120) for clindamycin/aminoglycoside; 87.5% (21/24) for metronidazole/gentamicin; 100% (13/13) for cefoxitin and 100% (10/10) for chloramphenicol/ampicillin.

2) Highlights of Individual Therapeutic and Prophylactic/[illegible]

   In this section, highlights of all U.S. studies (controlled, uncontrolled, therapeutic and prophylactic) as well as for controlled (therapeutic and prophylactic) European studies are provided. Additionally, in open label studies in Europe, 520 patients were treated with sulbactam/ampicillin - details of which are given in individual clinical summaries.

a) CONTROLLED THERAPEUTIC STUDIES

Clinical Study #15-1: A Blind Comparative Study of Parenteral Sulbactam/Ampicillin versus Moxalactam Administered in Cases of Biliary Tract Sepsis

In this study, parenteral sulbactam/ampicillin and moxalactam were equally effective (100%) in the bacteriological, clinical and overall [illegible] of patients with documented biliary tract sepsis.

Clinical Study #18-1: A Single Blind Comparative Study of Sulbactam/Ampicillin and Clindamycin/Tobramycin Combinations in Surgical Infections

Therapy with sulbactam/ampicillin eradicated a *Veillonella sp.* and a *Clostridium sp.* from the only evaluable patient accrued in this study.

Clinical Study #21-1: A Double-blind* Comparative Study of Parenteral Sulbactam Sodium/Ampicillin versus Clindamycin/Gentamicin Coadministered in Cases of Peritonitis Associated with Appendicitis

*Third party blinded by hospital pharmacy.

Sulbactam sodium and ampicillin were coadministered intravenously to 131 patients with preoperative diagnosis of gangrenous or perforated appendicitis. Ampicillin and sulbactam therapy eradicated 93.5% (150/170) of all organisms isolated from 62 evaluated patients. When examining the subsets by ampicillin susceptibility assignment, 89.6% (66/77) ampicillin resistant strains, 96.5% (56/58) ampicillin sensitive and 96.3% (26/27) intermediate organisms were eradicated. Susceptibility data were missing for eight cultures, however, these were eradicated also.

Sixty-four patients received clindamycin/gentamicin therapy: thirty-three patients were evaluated. All 82 isolated organisms were eradicated.

Side effects were experienced by 17/131 (13%) patients in the sulbactam/ampicillin treatment group and 4/65 (6.2%) in the clindamycin/gentamicin group. No patients were withdrawn from the study because of side effects.

Numerous abnormal laboratory values were recorded associated with both drug regimens in all likelihood attributable to the illness or surgical intervention.

__Clinical Study #23-1: A Blind Comparative Trial of Parenteral Sulbactam Sodium Coadministered with Ampicillin Versus Clindamycin/Gentamicin Coadministered in Treatment of Endomyometritis Encountered After Cesarean Section__

Bacteriological (96.6%), clinical (90.9%) and overall (81.8%) response rates achieved in the 11 evaluable patients who were treated with sulbactam/ampicillin demonstrate the efficacy of this combination in the treatment of a variety of infections. Comparative rates for the clindamycin/gentamicin group were: bacteriological 50/54 (92.6%), clinical 18/19 (94.7%) and overall 16/19 (84.2%).

__Clinical Study #25-1: A Comparative Study of Parenteral Sulbactam/ Ampicillin versus Ampicillin and Chloramphenicol in the Treatment of Meningitis in Infants and Children__

Bacteriological (100%), clinical (90.9%) and overall (90.9%) response rates achieved in the 11 evaluable patients who were treated with sulbactam/ampicillin demonstrate the efficacy of this combination in the treatment of meningitis in infants and children. Two of the 11 baseline isolates were ampicillin resistant strains of __H. influenzae__.

The single case considered a clinical and overall failure resulted from a premature decision to change therapy based on an early culture report. Subsequently, the CSF culture taken on the final day of sulbactam/ampicillin therapy was found to be negative for the ampicillin resistant __H. influenzae__ present before therapy.

Bacteriological, clinical and overall responses in the chloramphenicol/ampicillin treated group were 100%.

__Clinical Study #93-1: A Partially Blinded Comparative Study of Parenteral Sulbactam/ampicillin versus Cefoxitin Coadministered in Cases of Anaerobic and Polymicrobic Infections__

Bacteriological (97.2%), clinical (100%) and overall (92.3%) response rates achieved in the 13 evaluable patients who were treated with sulbactam/ampicillin demonstrate the efficacy of this combination in the treatment of a variety of infections including seven of eight cases associated with baseline pathogens found resistant __in vitro__ to the action of ampicillin alone. Comparative rates for the cefoxitin group were: bacteriological 37/39 (94.9%), clinical 13/13 (100%) and overall 13/13 (100%). Both regimens were well tolerated.

Clinical Study #98-1: A Single-blind Comparative Study of Parenteral Sulbactam/Ampicillin versus Clindamycin/Gentamicin Coadministered in Pediatric Cases of Intra-abdominal Anaerobic and Polymicrobic Infections

None of 5 patients treated with the sulbactam/ampicillin mixture were evaluable. The combination was well tolerated. There were no clinically significant side effects.

The administration of the clindamycin/gentamicin regimen eradicated 100% of the 17 baseline isolates obtained from 4 evaluable patients. One patient experienced diarrhea and a second had elevated SGOT/SGPT values, which returned to normal post therapy.

Clinical Study #89-1, #16-3, #90-1 #83-1, #88-1, #95-1, #87-1, #96-1, #91-1, #81-1: Protocol "A": A Third Party Blinded Multicenter Comparative Study of Parenteral Sulbactam/Ampicillin versus Clindamycin and Aminoglycoside Coadministered in Cases of Anaerobic and Polymicrobic Infections

Bacteriological (91.1%), clinical (92.2%) and overall (88.2%) response rates achieved in the 51 evaluable patients who received the sulbactam/ampicillin treatment regimen demonstrate the efficacy of this combination in the treatment of a variety of infections.

Eighty-six percent (55 out of 64) of the ampicillin resistant bacterial pathogens encountered were eradicated as a result of sulbactam/ampicillin therapy.

Comparative responses in the clindamycin/aminoglycoside group were: bacteriological 84.1%, clinical 86.4% and overall 84.1%.

The incidence and nature of side effects and laboratory abnormalities encountered in the two groups of patients were similar.

Clinical Study #29-4: Protocol "A": A Third Party Blinded Multicenter Comparative Study of Parenteral Sulbactam/Ampi[illegible] Coadministered in Cases of Intra-abdominal Infection and Related Infections of Gastrointestinal Tract (Conducted in Europe)

Bacteriological (90%), clinical (88.9%) and overall (88.9%) response rates achieved in the 27 evaluable patients who received the sulbactam/ampicillin treatment regimen demonstrate the efficacy of this combination in the treatment of a variety of infections.

Eighty-eight percent (30 out of 34) of the ampicillin resistant bacterial pathogens encountered were eradicated as a result of sulbactam/ampicillin therapy.

Comparative responses in the clindamycin/gentamicin group were: bacteriological 84.4%, clinical 100% and overall 90%.

The frequency and nature of both side effects and laboratory abnormalities observed in the sulbactam/ampicillin and clindamycin/gentamicin groups were similar.

Clinical Study #16-4, #95-2, #97-1, #82-1, #11-2, #94-1: Protocol "B": A Third Party Blinded Multicenter Comparative Study of Parenteral Sulbactam/Ampicillin versus Metronidazole/Aminoglycoside Coadministered in Cases of Anaerobic and Polymicrobic Infections

Bacteriological (92.9%), clinical (85.7%) and overall (85.7%) response rates achieved in the seven evaluable patients who received the sulbactam/ampicillin treatment regimen demonstrate the efficacy of this combination in the treatment of a variety of infections including three cases associated with baseline pathogens found resistant in vitro to the action of ampicillin alone. Comparative rates for the metronidazole/aminoglycoside group were: bacteriological 32/37 (86.5%), clinical 12/13 (92.3%) and overall 11/13 (84.6%). Both regimens were well tolerated.

Clinical Study #30-1, #31-1, #33-3: Protocol "B": A Third Party Blinded Multicenter Comparative Study of Parenteral Sulbactam/Ampicillin versus Metronidazole/Gentamicin Coadministered in Cases of Anaerobic and Polymicrobic Infections (Conducted in Europe)

Bacteriological (100%), clinical (90.9%) and overall (90.9%) response rates achieved in the eleven evaluable patients who received the sulbactam/ampicillin treatment regimen demonstrate the efficacy of this combination in the treatment of a variety of infections including all of 27 baseline pathogens found resistant in vitro to the action of ampicillin alone. Comparative rates for the metronidazole/gentamicin group were: bacteriological 46 out of 50 (92%), clinical 11/11 (100%) and overall 10/11 (90.9%). One patient from each treatment group was discontinued because of a side effect.

Clinical Study #91-2 and #12-3: Protocol "C": A Third Party Blinded Multicenter Comparative Study of Parenteral Sulbactam/Ampicillin versus Clindamycin in Cases of Anaerobic and Polymicrobic Infections

Therapy with clindamycin eradicated *Staph. aureus*, *Bacteroides melaninogenicus*, *Clostridium perfringens* and *Peptococcus*. sp. strains from two evaluable patients with osteomyelitis but failed to eradicate one strain of *Enterobacter cloacae*. One patient was an overall treatment success; the other a failure. The treatment regimen was well tolerated.

Clinical Study #33-2: An Open Comparative Study of the Efficacy of Sulbactam Plus Ampicillin Versus Gentamicin Plus Metronidazole in the Management of Intra-abdominal Sepsis

Forty patients with acute intra-abdominal infections requiring surgery (mainly appendicitis and peritonitis) were entered in this comparative study of sulbactam plus ampicillin versus gentamicin plus metronidazole. The sulbactam group (20 patients) received sulbactam (4 g daily; 1 g q.i.d.) for up to 8 days and the gentamicin group (20 patients) received gentamicin (250 mg daily; 80 mg t.i.d.) and metronidazole (1.5 g daily; 500 mg t.i.d.) for up to 10 days. All drugs were administered by the intravenous route.

At the end of treatment, 14/15 and 15/16 patients in the sulbactam and gentamicin groups respectively showed a satisfactory clinical response; at follow-up the proportions were 12/13 and 10/13 respectively. Eighteen of 18 and 16/18 pretreatment patnogens were eradicated in the sulbactam and gentamicin groups respectively at the end of treatment. Clinical plus bacteriological success was achieved in 10/10 and 8/10 sulbactam and gentamicin patients respectively at the end of treatment.

Side effects in the sulbactam group were restricted to pain at the injection site in 3 patients associated with phlebitis in one; one further patient had phlebitis. In the gentamicin group, 7 patients experienced pain at the injection site. One patient also had tinnitus. Four patients (one in sulbactam group and 3 in gentamicin group) died from causes unrelated to the treatment.

Two patients were withdrawn because of possible gentamicin-induced nephrotoxicity and another patient treated with gentamicin and metronidazole showed eosinophilia.

Clinical Study #84-1: An Open Comparative Study of the Combination of Sulbactam with Ampicillin Versus Cefotaxime in Serious Acute Soft Tissue/Joint Bone Infections

Twenty-one patients with serious bone or soft tissue infections were treated with either sulbactam plus ampicillin (11 patients) or with cefotaxime (10 patients). Patients in the sulbactam group received intravenous infusions of sulbactam (3 g daily; 1 g t.i.d.) plus ampicillin (6 g daily; 2 g t.i.d.) for 8-16 days (mean 13.9). Patients in the cefotaxime group received cefotaxime (6 g daily; 2 g t.i.d.) also by intravenous infusion for 2-16 days (mean 12.4).

Of pathogens isolated pretreatment, 11/12 and 6/8 were eradicated at the end of treatment in the sulbactam and cefotaxime groups respectively including 6/7 in the former resistant to ampicillin. At the end of treatment, all 11 sulbactam patients and 7/8 cefotaxime subjects showed acceptable clinical improvement.

Five patients in the sulbactam/ampicillin group experienced mild to moderate side effects (diarrhea, nausea, skin reaction and yeast infection [2 patients] respectively). In the cefotaxime group one patient complained of mild itching.

Although rises in SGOT and SGPT values were recorded in several patients in both groups, many were transitory and were considered therefore attributable to the infection and/or surgery coupled with a history of alcohol abuse in some cases. In one patient, however, who received cefotaxime the rise was greater and not readily explained. Increased alkaline phosphatase levels and falls in red cell values were considered attributable to the disease and surgery and occurred in both treatment groups.

Clinical Study #84-[illegible]: An Open Comparative Study to Determine Any Effects of Sulbactam on Glucose Metabolism in Diabetic Subjects

Twenty-six diabetic patients, all with skin and soft tissue infections entered the study. Three patients were treated twice, once in each group.

In the first group, 15 patients received intravenous sulbactam/ampicillin (mean duration 8.7 days) usually followed by sultamicillin orally. In the second group, 14 patients were given intravenous flucloxacillin plus ampicillin (mean duration 6.6 days) followed in most cases by oral treatment with the same antibiotics.

Eighteen patients, 9 in each group had glucagon challenges at start and end of treatment. Glucose and C-peptide AUCs and change to peak concentrations did not differ significantly between the sulbactam/ampicillin group and the flucloxacillin/ampicillin group between the first and second challenges. Percentages of abnormal glucose readings, for both high and low values, were similar in each treatment group.

A number of patients had severe ischemic disease pre-existing the infection and amputations were necessary. In no case was amputation the result of failure of trial therapy. Where pre-existing ischemic disease did not compromise the outcome, both treatments showed a satisfactory response in 8/9 patients in each group.

In the sulbactam/ampicillin group 4/4 pathogens from 4 patients, including 2 resistant to ampicillin, were eradicated but one relapsed while oral therapy continued. Five pathogens from 4 patients in the comparative group, including 4 resistant to ampicillin were eradicated.

One patient [illegible]
Other side effects, mainly connected with the injection site, were transient and minor.

Some laboratory test abnormalities which occurred during treatment were in all probability related to the underlying disease and infection; for others no explanation was apparent. These included increases in blood urea (plus creatinine in one case) in 4 patients on sulbactam/ampicillin and one patient on flucloxacillin/ampicillin. Two patients in the latter group showed elevated SGOT values. One, who also had decreased red blood cell parameters, required a transfusion.

b) <u>CONTROLLED PROPHYLACTIC/PERIOPERATIVE STUDIES</u>

<u>Clinical Study #02-4: An Observer-Blind Comparative Study of the Efficacy of Parenteral Sulbactam/Ampicillin Compared to Cefazolin in Preventing Infection Following Elective Surgery</u>

In this study of 146 patients perioperative treatment with sulbactam and ampicillin was equally effective as cefazolin in the prevention of postoperative infections.

Clinical Study #19-1: A Third Party Blinded Comparative Trial of Parenteral Sulbactam Coadministered with Ampicillin and Placebo in Prevention of Postoperative Infections Encountered After Cesarean Section

In this study dealing with 113 patients, perioperative treatment with sulbactam/ampicillin regimens of 1.0gm/2.0gm and 0.5gm/1.0gm produced significant ($p \leq .001$) reductions in the incidence of post-cesarean section infections as compared with placebo prophylaxis.

Clinical Study #24-1: A Prospective, Randomized, Observer-blind Study of the Efficacy of Sulbactam/Ampicillin Compared to Cefoxitin in Preventing Infection Following Transurethral Surgery

In 103 evaluable patients with preoperative sterile urine who underwent transurethral surgery, perioperative treatment with 0.5gm sulbactam and 1.0gm ampicillin reduced the incidence of postoperative infections to approximately 19% while perioperative treatment with 1.0gm cefoxitin reduced the same incidence to approximately 10%. No statistically significant difference was found between the two results.

The above analysis was based on an assumption that any bacteriuria was evidence of postoperative infection. An independent analysis of this study has been done by the investigator utilizing standard infection criteria for significant bacteriuria ($\geq 10^5$ CFU/ml in clear catch urine and $\geq 10^4$ CFU/ml in catheterized samples. Based on this analysis, he reports postoperative infections in 8% of the evaluable patients treated with sulbactam/ampicillin and in 4% of the evaluable patients treated with cefoxitin. He also concluded that sulbactam/ampicillin and cefoxitin were equally efficacious and safe in prevention of postoperative infection in transurethral surgery.

Clinical Study #33-1: An Open Comparative Study to Assess the Efficacy of Sulbactam Plus Ampicillin, Cefazolin Plus Metronidazole, and Placebo, in the Prophylaxis of Abdominal Wound Infections

A single dose of sulbactam/ampicillin (500 mg/500 mg, 125 patients), cefazolin/metronidazole (1,000 mg/50 mg, 126 patients) or placebo (132 patients) was administered by intravenous bolus injection and 30 minute infusion within 30 minutes prior to the start of clean, contaminated abdominal surgery. Wound infections developed in only one case on cefazolin/metronidazole, none on sulbactam/ampicillin, but 11 cases in the placebo group. Overall, pathogens were isolated from 8/12 wounds, all in the placebo group. Single dose prophylaxis with sulbactam/ampicillin or cefazolin/metronidazole significantly ($p < 0.01$) reduced the incidence of postoperative wound infections. There was no difference in the length of stay in the hospital of patients in the 3 groups and the incidence of infection at other sites was not affected by treatment.

There were no side effects related to treatment. Laboratory safety parameters were not monitored.

Clinical Study #58-1: A Single Blind, Comparative Study to Assess the Efficacy of Sulbactam Plus Ampicillin, Metronidazole Plus Ampicillin, and Placebo, in the Prophylaxis of Wound Infections After Clean or Clean Contaminated Gynecological Surgery

A single dose of sulbactam + ampicillin (500 mg + 500 mg, 112 patients), metronidazole + ampicillin (1,000 mg + 500 mg, 116 patients), or placebo (117 patients) was administered before clean or clean contaminated gynecological surgery. Metronidazole and placebo were administered by suppository 1-2 hours before the start of the operation and sulbactam and ampicillin by slow intravenous injection at the time of induction of anaesthesia. The three treatment groups were well matched for known risk factors for infective complications - age, obesity, anemia, postmenopausal status and operation type. During the 7 days immediately after surgery, wound infections developed in 4/87, 3/88 and 19/83 patients in the sulbactam/ampicillin, metronidazole/ampicillin and placebo groups respectively. No further wound infections were recorded at follow-up 40-60 days after operation. Pathogens were isolated from 2/4, 0/3 and 11/19 wounds in the sulbactam/ampicillin, metronidazole/ampicillin and placebo groups respectively. The incidence of febrile morbidity was reduced from 18/97 patients in the placebo group to 4/100 and 2/98 in the sulbactam/ampicillin and metronidazole/ampicillin groups respectively. The mean duration of stay in hospital was 10.6, 9.8 and 11.8 days in the sulbactam/ampicillin, metronidazole/ampicillin and placebo groups respectively. Four patients in the placebo group with infected wounds had extended stays in the hospital.

Seven patients in the sulbactam/ampicillin group reported treatment-related mild nausea. In the metronidazole/ [illegible]icillin [illegible] a rash) experienced side effects. In the placebo group there were 2 patients who reported nausea and one patient with moderate diarrhea.

Laboratory tests were performed once only preoperatively before drug administration. Postoperative treatment samples were not obtained.

It was concluded that prophylaxis with either sulbactam plus ampicillin or metronidazole plus ampicillin signficiantly reduced the incidence of wound infections, febrile morbidity, but did not affect the incidence of postoperative infections at other sites.

Clinical Study #62-2: An Open, Comparative Study To Compare the Efficacy of Sulbactam Plus Ampicillin and Cefoxitin in the Prophylaxis of Infective Complications After Colorectal Surgery

One hundred three patients undergoing colorectal surgery were randomized into two groups to receive 24 hours perioperative and postoperative prophylactic antibiotic therapy with either sulbactam 1,000 mg plus ampicillin 1,000 mg or cefoxitin 2,000 mg 6-hourly for 4 doses. The groups were well matched in respect of known risk factors and operative procedures. Five of 36 assessable patients in sulbactam/ampicillin group developed wound infections in the immediate postoperative period, and a further 4/25 assessable later, had later wound infections. In the cefoxitin group, 4/39 had early wound infections and 4/28 later wound infections. Four infections in each group were classed as major. Bacteria were isolated from 7/9 sulbactam/ampicillin wound infections and 4/8 cefoxitin wound infections. Sixteen other infective complications occurred in both groups in the first 10 days postoperation and a further 3 in each group developed later infective complications. Other complications of surgery were recorded in 14 and 8 patients respectively in the 2 groups, some of which were surgical problems ultimately leading to death.

Both treatments were well tolerated. One patient on sulbactam/ampicillin had venous induration at the site of infusion. Most changes in laboratory safety tests were attributable to the extensive surgery and were similar in the 2 treatment groups; 2 patients on sulbactam/ampicillin had slightly raised SGOT values and minor elevation in alkaline phosphatase was seen in 2 sulbactam/ampicillin and 3 cefoxitin patients. Increased total bilirubin values were recorded in 4 sulbactam/ampicillin and 2 cefoxitin patients.

It was concluded that sulbactam plus ampicillin was equally efficacious as cefoxitin in controlling postoperative complications following colorectal surgery.

Clinical Study #75-1: A Single-blind Study to Compare the Efficacy of Sulbactam Plus Ampicillin and Placebo in the Prophylaxis of Postoperative Infection in Patients Undergoing Termination of Pregnancy by Vacuum Aspiration

This is an interim report of a study still in progress. A single dose of sulbactam 500 mg plus ampicillin 1,000 mg (52 patients) or placebo (54 patients) was administered by slow intravenous injection immediately before the start of vacuum aspiration for termination of pregnancy. The 2 treatment groups are well matched in respect of age, presence of intrauterine devices and baseline bacteriological findings. A single dose of sulbactam/ampicillin reduced the incidence of frank or suspected endometritis. During the 7 days immediately after operation, 2/52 and 4/53 patients in the sulbactam/ampicillin and placebo groups respectively were diagnosed as having endometritis and another 8 and 12 respectively had symptoms indicative of infection. Two patients in the placebo group developed endometritis 17 and 30 days after the procedure.

No treatment-related side effects were reported in either treatment group. There were no clinically relevant laboratory test abnormalities attributable to treatment.

Clinical Study #79-1: An Open, Comparative Study to Compare the Safety and Efficacy of Sulbactam Plus Ampicillin, and Gentamicin Plus Metronidazole, in the Prevention of Infective Complications After Colorectal Surgery

To date, 27 cases undergoing colorectal surgery have been treated prophylactically with either 4 doses at 6 hour intervals of sulbactam 1.0 g plus ampicillin 2.0 g or 3 doses at 8 hour intervals of gentamicin 80 mg plus metronidazole 500 mg. At present the 2 treatment groups are not comparable with respect to age, sex or operative procedures. In the first week postoperation, 4 minor wound infections have been observed in 11 assessable patients in the sulbactam/ampicillin group and one wound infection in the 12 assessable gentamicin/metronidazole patients. Two patients in the sulbactam/ampicillin group and one in the gentamicin/metronidazole group had urinary tract infections in the same period only the latter being confirmed microbiologically. There were no further infections in the follow-up period. There was no difference in the duration of hospital stay in the 2 treatment groups.

One case on sulbactam/ampicillin who had persistent oozing of blood after 8 hours (2 doses of sulbactam/ampicillin) required further surgery. No abnormality of bleeding time or clotting parameters were found. One patient also on sulbactam/ampicillin had oral candidosis, attributable to his concomitant steroid therapy. Laboratory safety tests showed no treatment related changes.

c) <u>OPEN, NON-COMPARATIVE STUDIES</u>

<u>Clinical Study #02-1: An Open Study of Parenteral Sulbactam Sodium/Ampicillin</u>

Sulbactam sodium/ampicillin administered intravenously every 6 hours was effective in the treatment of a variety of infections caused by ampicillin resistant and susceptible organisms. The combined therapy eradicated 97.46% (38/39) of all organisms isolated from twenty-six patients; 93.7% (15/16) of ampicillin resistant and 100% (19/19) of ampicillin sensitive organisms were eradicated. Clinical cure was obtained in 96.2% (25/26) of patients. The drugs were well tolerated.

<u>Clinical Study #04-2, 10-1, 20-1: A Noncomparative Study of Sulbactam Sodium/Beta Lactam Antibiotic Coadministered in Clinical Infections</u>

Parenteral coadministration of sulbactam sodium and penicillin G achieved satisfactory clinical and bacteriological responses in the treatment of infections caused by both penicillin or ampicillin resistant and susceptible strains of organisms. Of the 65 isolates, 36 (55.4%) were resistant. Twenty-nine of thirty-six resistant organisms (80.6%) were eradicated by the combination therapy.

<u>Clinical Study #12-2: An Open Study of Parenteral Sulbactam Sodium/Ampicillin</u>

Sulbactam sodium combined with ampicillin and administered by intravenous infusion was effective in the treatment of a variety of infections caused by ampicillin resistant and susceptible organisms. The combined therapy eradicated 87.0% (20/23) of all organisms isolated from 12 patients; 66.7% (4/6) of ampicillin resistant and 93.3% (14/15) of ampicillin sensitive organisms were eradicated (sensitivity data were not available for 2 organisms).

Two adverse reactions (phlebitis and dry skin) were reported. Four instances of elevated SGOT and one of increased alkaline phosphatase were observed.

Clinical Study #13-1: A Non-Comparative Study of Parenteral Sulbactam Sodium (CP-45,899) Co-Administered with Ampicillin in a Variety of Clinical Infections.

[illegible]enteral [illegible]-administration of 500 mg sulbactam sodium [illegible] 500 mg ampicillin every six hours for eight days [illegible]ulted in complete clinical remission of acute [illegible]llulitis in one patient. However, a baseline pathogen [illegible] not isolated, and therefore, this case was not [illegible]valuated. A second patient received a non-protocol antibiotic in addition to sulbactam/ampicillin and was not evaluated.

There were no side effects or abnormal laboratory values due to sulbactam or ampicillin therapy.

Clinical Study #14-1: A Noncomparative Study of Parenteral Sulbactam/Ampicillin Coadministered in Gynecological Infections

Administration of 1.0gm sulbactam and 2.0gm ampicillin by intravenous infusion every 6 hours was successful in the eradioation of 84/86 bacterial strains isolated at baseline from 30 patients with gynecological infections (postpartum endometritis). Overall satisfactory responses were obtained in 24/30 (80%) of patients. One of the patients with unsatisfactory responses received only 48 hours of therapy.

Clinical Study #16-1: A Noncomparative Study of Parenteral Sulbactam Sodium and Ampicillin Coadministered in Clinical Infections

Sulbactam [illegible] combination was administered intravenously to patients with a variety of severe clinical infections. The combined therapy eradicated 19/23 (82.6%) of the organisms isolated from 15 evaluated patients. Ampicillin susceptibility data were missing for 17/23 pathogens, however, 2/2 ampicillin resistant (100%), 3/4 (75%) ampicillin sensitive strains were eradicated by the combined therapy. Thirteen of 15 evaluated cases were considered clinical cures.

No side effects were reported.

A number of abnormal laboratory findings was recorded in all likelihood related to the nature of this severely ill patient population.

Clinical Study #17-1: A Therapeutic Trial of Epiglottitis (A Noncomparative Study of Parenteral CP-45,899 in Combination with Ampicillin)

Sulbactam sodium/ampicillin administered parenterally every six hours was highly effective in the treatment of epiglottitis caused by *H. influenzae*. Regardless of the ampicillin susceptibility of the pathogen, the combined therapy eradicated all the causative organisms and effected a complete clinical remission in all patients.

Clinical Study #98-2: An Open Study of the Efficacy and Safety of Sulbactam/Ampicillin Administered Parenterally and Sultamicillin Administered Orally in Childhood Skeletal Infections

Therapy with sulbactam/ampicillin followed by oral treatment with sultamicillin eradicated the *Hemophilus influenzae* strain isolated from a case of [illegible] arthritis of the knee in the only bacteriologically evaluable patient reported in this study.

8. CONCLUSIONS

Sulbactam/ampicillin is a new combination antimicrobial of two beta-lactams for parenteral (intravenous or intramuscular) treatment of bacterial infections in a variety of clinical indications.

Ampicillin is a time-tested broad-spectrum antimicrobial with an established record of safety. The increasing incidence of beta-lactamase producing pathogens has, however, limited ampicillin's clinical usefulness. Sulbactam, a simple derivative of the basic penicillin nucleus does not itself have a useful antibacterial activity, however, it is an irreversible inhibitor of several important beta-lactamases. The combination of ampicillin and sulbactam restores ampicillin to its former utility of activity including beta-lactamase producing strains of Staphylococci, _H. influenzae_, Bacteroides spp. and many Enterobacteriaceae.

A potent synergistic activity has also been demonstrated in _in vitro_ experiments against organisms with constitutive beta-lactamase such as _K. pneumoniae_ and _P. vulgaris_ which were always resistant to ampicillin alone.

The combination of sulbactam and ampicillin is a particularly promising antimicrobial for the treatment of polymicrobial (aerobic and anaerobic) infections frequently involving beta-lactamase producing _B. fragilis_.

No untoward cardiovascular effects have been observed in animal experiments or clinical trials.

Sulbactam pharmacokinetics in man are very similar to those of other beta-lactam antimicrobials. Sulbactam has virtually no effect on the kinetics of coadministered ampicillin suggesting that the usual dose regime of ampicillin need not be adjusted to the coadministration of sulbactam. Sulbactam is primarily eliminated by urinary excretion; more than 75% of a dose is recovered in urine. Tubular secretion plays a major role in its elimination and hence probenecid extends the half-life of sulbactam. Similarly, half-life is extended in patients with impaired renal function. Biliary excretion of sulbactam in man is a minor pathway of elimination. The half-lives of ampicillin and sulbactam are both approximately one hour. They both distribute with comparable rates into similar apparent volumes of distribition. Low protein binding (38%) of sulbactam predicts rapid diffusion from blood to extravascular tissues.

An extensive series of safety evaluation [illegible] in experimental animals. The results of these studies and of reproductive, teratology, and neonatal studies have been discussed in Section 2-3.D.3. "Safety Evaluation Studies." Liver is the only target organ demonstrated for sulbactam. The most characteristic effect of sulbactam in both dogs and rats, when administered in large amounts (400 mg/kg) over 30 days, was the deposit of hepatocellular glycogen. This effect (glycogenosis) is reversible, dose and time related. This effect is not expected to develop at the therapeutic doses and corresponding plasma levels attained during the relatively short periods of treatment in man.

The clinical program comprised 287[illegible] patients entered into the efficacy and safety evaluation studies. There were 1764 patients treated with sulbactam/ampicillin and 1108 treated with comparative antimicrobials. In the therapeutic trials 1185 patients were assigned to sulbactam/ampicillin therapy. An overall satisfactory response was achieved in 88.3% (565/640) of the evaluated patients treated with sulbactam/ampicillin.

In controlled comparative trials, sulbactam and ampicillin was equally efficacious as control antimicrobials (clindamycin, gentamicin, cefoxitin, and ampicillin chloramphenicol).

Sulbactam/ampicillin was shown to be highly efficacious in treating infections caused by beta-[illegible] [illegible] influenzae, Klebs. pneumoniae, Staph. aureus, Staph. epidermidis, E. coli, Branham. catarrhalis, Prot. spp., Enterobacter spp., Morganella morgani, Acin. calcoaceticus var. antitratus and anaerobic Bacteroides spp. and Peptococcus spp. In addition, mixed infections with a polymicrobic flora containing ampicillin susceptible micro-organisms responded well to sulbactam/ampicillin treatment due to its ampicillin content.

One hundred ninety five drug related adverse reactions occurred in 9% (153/1764) of patients treated with sulbactam/ampicillin. The most common adverse reaction was pain on injection site 3.6% (64/1764) followed by diarrhea 1.9% (34/1764) and phlebitis 1.2% (22/1764). All other adverse reactions had an incidence of less than 1%.

In most cases the reported adverse reactions were mild to moderate in severity and only in 0.7% (13/1764) cases treatment with sulbactam/ampicillin was discontinued because of an adverse reaction.

In controlled comparative trials the incidence and severity of adverse reactions was nearly identical for sulbactam/ampicillin and the control antimicrobials.

The most frequently detected laboratory abnormalities were elevations of SGOT 9.3% (113/1216), SGPT 8.9% (84/947), LDH 11.3% (44/390), and alkaline phosphatase 3.4% (43/1249). In a subset of cases entered randomly into controlled comparative trials, the incidence of respective abnormal values in sulbactam/ampicillin treated patients for SGOT, SGPT, LDH and alkaline phosphatase were 11.4% (50/440), 12.[illegible]% ([illegible]/379), 10.4% (26/24[illegible]), and 2.7% (12/441). The incidence of laboratory abnormalities recorded for the same tests in association with other "control" antimicrobials was nearly identical: 12.2% (40/[illegible]), [illegible]% (32/278), 12.3% (19/155), and 2.8% (9/327).

In summary, sulbactam/ampicillin is an effective and safe antimicrobial combination, particularly suitable for the treatment of infections caused by beta-lactamase producing pathogens and the treatment of polymicrobial (aerobic and anaerobic) infections where one or more beta-lactamase producing pathogens commonly are involved.

DRUG CONTROL REVIEW NOTES -

NDA 50-608

Rx: Rx

DOSAGE FORM: Dry powder filled vials for IV & IM inspection

	(1)	(2)	(3)	(4)
ampicillin sodium	2.0g	1.0g	0.5g	0.25g
sulbactam sodium	1.0g	0.5g	0.25g	0.125g

SPONSOR: Pfizer Inc.
Eastern Point Road, Groton, Connecticut 06340

SUBMISSION REVIEWED:

a. Original dated: 4/18/85

b. Amendments dated:

c. Providing for:

NAMES:

a. TRADE: Unasyn

b. NON-PROPRIETARY: Sterile ampicillin sodium/sulbactam sodium

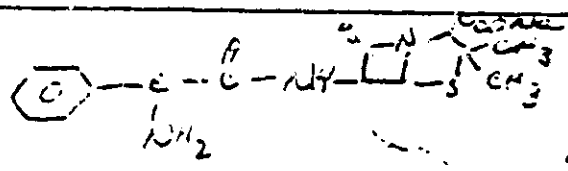
c. CHEMICAL: Monosodium (2S,5R,6R)-6-[(R)-2-amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate and sodium (2S,5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate 4,4-dioxide.

d. ESTAB: Ampicillin sodium/sulbactam sodium

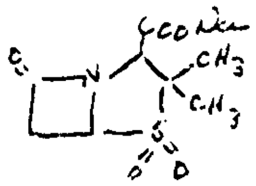
e. USAN: Ampicillin sodium/sulbactam sodium

f. WHO:

STRUCTURAL FORMULA:



ampicillin sodium



sulbactam sodium

RELATED NDA, IND, MF, FORM 5's: IND 13,940; Form 6#s 61-789, 61-618, 62-056, 60-129 and 62-552.

NDA 50-608
Page 2

REMARKS:

CONCLUSIONS: Labeling for trays needs to be submitted. Labeling on vials needs some revisions, package insert needs some revisions, additional stability data needed.

(Reviewer) James R. Ramsey
James R. Ramsey
Microbiologist
HFN-815
3/27/86

cc: Orig. NDA 50-608
HFN-815
HFN-815/CSO
HFN-178
HFN-235
HFN-815/JRRamsey/~~3/27/~~86/dh
R/D: init. by RNorton/7/ /86