Evaluability Definitions

(1) Evaluable population

To be considered fully evaluable for clinical response, a subject must have :

a. an intra-abdominal focus of established infection documented by operative intervention or by a radiographically-controlled drainage procedure

b. signs and symptoms of an intra-abdominal infection

An indeterminate *clinical* outcome assessment was made (i.e., made nonevaluable), if the subject fulfilled any of the following criteria:

a. Insufficient therapy: received < 5 days of double-blind therapy unless considered a failure

b. inapplicable diagnosis (i.e. subject did not meet entry criteria for intra-abdominal infection).

c. Concomitant systemic antibacterials given for intercurrent illness. However, if a subject receives additional antimicrobial agents for nosocomial infections outside the abdomen ≥ 5 days into the trial, the reason should be documented by the principal investigator or his designate and noted on the subject's Case Report Form. If no evidence of an intra-abdominal infection, nor evidence of a recurrent intra-abdominal infection during the subsequent clinical course exists, then this subject may be considered evaluable and, accordingly, a clinical cure.[3]

d. Missing post-baseline clinical assessments: no visit at evaluation point unless subject was previously designated as a treatment failure.

e. Inadequate initial operative procedure. An operation is considered inadequate if not all communications between the gastrointestinal tract and the peritoneal cavity are closed and/or if necrotic intestine is left and/or if an infected collection was missed at the initial drainage. Prior to the blind being broken, a panel of investigators and the sponsor will consider those cases which have questionable evaluability. Operative notes or percutaneous drainage notes will be reviewed and a decision will be rendered on the evaluability of these subjects.

f. Death: subjects who die within 48 hours after initiation of double-blind therapy.

g. if appropriate, other criteria may be added.

An indeterminate *bacteriologic* outcome assessment was made (i.e., made nonevaluable), if the subject fulfilled any of the following criteria:

---

[3]Solomkin JS, Hemsell DL, Sweet R, Tally F, Bartlett J. Evaluation of new anti-infective drugs for the treatment of intra-abdominal infections. *Clin Infect Dis* 1992; 15(**Suppl** 1):S33-S42.

a. relevant post-baseline cultures are not obtained, unless it is a result of the absence of adequate purulent culture material (to be considered presumptive microbiologic eradication as defined below) or concomitant antibiotic use due to bacteriologic persistence

b. concomitant antibiotic use for treatment of an intercurrent illness

c. the subject was not considered clinically evaluable.

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(2) Modified Intent-to-Treat population (protocol defined)
To be evaluable for the MITT analysis,

Subjects with inappropriate primary diagnoses (e.g., no clinical signs or symptoms at baseline, or having entered the study more than once) will be excluded. Otherwise, all randomized subjects will be included in the modified ITT analysis. Subjects with no clinical information after the baseline evaluation will be considered as clinical treatment failures.

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Clinical Intent-to-Treat Subjects (from study summary)

The clinical intent-to-treat subjects subset included those subjects in the all randomized subjects subset who had confirmed intra-abdominal infection and underwent surgery or percutaneous drainage at baseline. Some subjects in this subset may never have received any study medication.

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Bacteriological Intent-to-Treat Subjects (from study summary)

The bacteriological intent-to-treat subjects subset included those subjects in the clinical intent-to-treat subjects subset with at least one pathogen identified at baseline in either peritoneal fluid or blood culture. Subjects in this subset may never have received any study medication.

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Efficacy Analyses

According to a November 1995 protocol amendment, the primary efficacy parameter:

will be *sponsor-defined* clinical response at follow-up (day 30).

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The same amendment states :

The following secondary efficacy outcome parameters will be tabulated and compared between treatment groups:

- *sponsor-defined* clinical response at end of double-blind therapy
- *investigator-defined clinical response at the end of double-blind therapy and at follow-up*
- *sponsor-defined organism outcome at end of treatment and at follow-up*
- changes in baseline APACHE score on days 4, 7, 10, and 14 after start of double-blind therapy
- time post-operatively spent in the hospital (days)
- time of post-operative fever (days)
- time to recovery (days)
- duration of intravenous therapy (days)
- proportion of subjects with nosocomial infection
- proportion of subjects receiving additional antibiotics

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Schedule of Study Evaluations

Study day Allowable Window: Treatment Period Day 1 to Day 14[a] Follow-up period Day 15 to Day 42	Day 1 -48 hours	Day 4 Day 3-5	Day 14[a] Day 10-14	Day 30 Day 28-42
Informed consent	X			
Demographic information	X			
Physical examination of the abdomen[b]	X----------	----------	----------X	X
Maximum body temperature[b]	X----------	----------	----------X	X
Vital signs	X	X	X	X
Concomitant medication	X	X	X	X
APACHE scoring	X	X[c]	X	
Dosing record		X	X	
Clinical signs & symptoms[b]	X----------	----------	----------X	X
Assessment of bowel function[b]	X----------	----------	----------X	X
Microbiology culture & sensitivity				
• blood	X	X[d]	X[d]	X[d]
• peritoneal	X[e]			
Safety laboratory tests				
• hematology	X	X	X	abn
• biochemistry	X	X	X	abn
• urinalysis	X	X	X	abn
• pregnancy test[f]	X			
Adverse events	X----------	----------	----------X	X
Investigator's assessment of clinical response[g]			X	X
Time of recovery	X----------	----------	----------X	X
Health care resource utilization	X----------	----------	----------X	X

[a]or end of double-blind therapy if sooner
[b]performed daily during the hospitalization period
[c]recorded also on days 7 and 10
[d]only if clinically indicated (e.g., time of discontinuation or previously positive culture)
[e]or up to a 12-hour period after start of therapy
[f]to be done locally for women of child bearing potential
[g]and to be done at the time of discontinuation, if applicable
abn=to be done only if abnormal at previous visit or clinically significant adverse event

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8.3 Study Results

MO Comment : The Medical Officer reviewed the applicant's patient data and, in general, agreed with their assignment of patients to populations and outcome responses. Therefore, for the purposes of this review, the MO's and applicant's efficacy and safety populations are the same.

INVESTIGATORS:

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5133	Dennis Mikolich, MD
	5204	Stanley Klein, MD
	5229	Michael Neill, MD
	5429	John Yatsu, MD
	5431	Steven Mintz, MD
	5486	David Borgstrom, MD
	5495	George Mueller, MD
	5497	Joseph Wentzky, Jr, MD
	5524	C. Gene Cayten, MD
	5525	David Smith, MD
	5526	Gene Coppa, MD
	5529	Vinod Dhawan, MD
	5530	Philip Donahue, MD
	5532	Blaine Enderson, MD
	5533	Michael Esser, MD
	5534	Richard Greenberg, MD
	5535	David Longworth, MD
	5537	Luis Jauregui, MD
	5542	Carey Page, MD / Ronald Stewart MD
	5545	Robert Martindale, MD
	5549	Michael Metzler, MD
	5550	Ronald Simon, MD
	5552	John Oropello, MD
	5553	Russell Postier, MD
	5557	William Stahl, MD
	5560	Richard Wait, MD
	5562	Bienvenido Yangco, MD
	5563	Thomas Berne, MD
		Albert Yellin, MD
	5599	Jefferson Stowers, MD
	5606	Robert Gainer, II, MD
	5608	Lawrence Nastro, MD
	5610	Jon White, MD
	5613	Peter Krumpe, MD
	5614	Amir Neshat, MD
	5615	Kathaleen Porter, MD
	5616	David Redfield, MD

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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States (continued)	5617	Joseph Solomkin, MD
	5619	Barry Miskin, MD
	5661	Norman Zinner, MD
	5739	James Wagner, MD
	5761	John Mazuski, MD
	5910	Joseph Portoghese, MD
	5931	Carol Kemper, MD
	5970	Alan Sugar, MD
	5998	Kenneth Courington, MD
	6006	Richard Kohler, MD
	6012	Corrado Marini, MD
	6044	Alexander Robbins, MD
	6046	E. Robert Harris, MD
	6047	Joseph Scoma, MD
	6048	Mark Sherman, MD
	6052	Craig Schaefer, MD
	6053	Ronald Nichols, MD
	6055	Jan Elston, MD
	6067	Larry Danziger, PharmD
	6068	Leon Smith, MD
	6069	Judith Wolf, MD
	6090	Burke Cunha, MD
	6099	Manuel Ramirez, MD
	6100	Vinod Rustgi, MD
	6107	Dana Edwards, MD
	6151	Gregory Timberlake, MD
	6155	Ellis Caplan, MD
	6170	Eduardo Gonzales, MD
	6246	Michael Hellinger, MD
	6287	Nicholas Price, MD
	6344	William O'Riordan, MD
	6367	Del Dehart, MD
	6380	John Dawson, MD
	6381	Bruce Harris, MD
	6382	Jay Harviel, MD
	6383	Carol Leitner, MD
	6395	Gaylord Kavlie, MD
	6398	Patrick White, MD
	6409	Ronald Jackson, DO
	6424	H. Scott Bjerke, MD
	6425	Edward Condon, MD
	6431	Martin Schrieber, MD
	6498	Thomas Lawson, Jr., MD
	6499	Robert Cohen, MD
France	5187	Dr. Didier Grange
	5199	Dr. Paul Teniere
	5990	Dr. Francois Fraisse
	6013	Dr. Georges Goursot
	6014	Dr. Francis Bur

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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
France (continued)	6016	Dr. Jean Dupeyron
	6017	Dr. Philippe Duvaldestin
	6018	Dr. Luc Guyot
	6019	Dr. Claude Jacquot
	6020	Dr. Patrick De Rohan Chabot
	6095	Dr. G. Kohlmann
	6311	Dr. Patrick Cougard
	6436	Dr. Ghassan Ferzli
	6437	Dr. Fariborz Hakami
	6439	Dr. Jean-Michel Kerrenneur
	6440	Dr. Michel Ossart
	6441	Dr. Jean-Claude Otteni
	6442	Dr. Philippe Lallemant
	6444	Dr. Christian Virenque
Canada	5155	Sylvie Trottier, MD
	5598	Frederick Brenneman, MD
	5921	Frank Baillie, MD
	6365	Marvin Gerson, MD
	6384	Jean Ledoux, MD
	6451	Claude Lemieux, MD
	6465	Jean-Francois Bellemare, MD
	6467	Vivian Mcalister, MD
	6468	Murray Girotti, MD
Poland	6517	Dr. Otmar Gedliczka
	6518	Dr. Zygmunt Mackiewicz
	6521	Dr. Bogdan Lazarkiewicz
	6522	Dr. Bruno Szcygiel
	6523	Dr. Andrzej Karwowski
	6524	Dr. Wojciech Noszczyk
Belgium	6092	Dr. Bernard Broze
	6093	Dr. Claude Chastel
	6496	Dr. Yves Van Laethem
United Kingdom	6255	Dr. Roger Leicester
	6256	Dr. Eric Taylor
	6258	Dr. Peter Donaldson

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The study was conducted in several countries and many centers were enlisted (120 total centers: 80 USA, 9 Canada, and 31 Europe).

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Number of Patients Evaluated in Each Group		
	Alatrofloxacin ↓ Trovafloxacin	**Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid**
Randomized	204	210
Randomized, not treated	3	3
All Treated	201 (100%)	207 (100%)
Completed Treatment	167 (83%)	170 (82%)
Completed Study	181 (90%)	184 (89%)
Evaluated for Efficacy[a]		
Clinical Intent-to-Treat	200 (98%)	199 (95%)
Clinical Intent-to-Treat with Abscesses	118 (58%)	102 (49%)
Clinical Intent-to-Treat with Peritonitis	111 (54%)	115 (55%)
Clinically Evaluable[b]	156 (76%)	152 (72%)
Clinically Evaluable with Abscesses	96 (47%)	82 (39%)
Clinically Evaluable with Peritonitis	87 (43%)	85 (40%)
Bacteriologically Intent-to-Treat	171 (84%)	164 (78%)
Bacteriologically Evaluable	135 (66%)	131 (62%)
Assessed for Safety		
Adverse Events	201 (100%)	207 (100%)
Laboratory Tests	198 (99%)	205 (>99%)

a Based on the number of randomized subjects.
b Evaluability determined at the end of study.

A total of 414 patients (204 Trovan vs. 210 Primaxin → Augmentin) were randomized into the study. There was no significant difference between treatment arms in the proportion represented in the various study populations.

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Summary of Baseline Demographic Characteristics

	Alatrofloxacin ↓ Trovafloxacin	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanic Acid
	Number and Percentage (%) of Subjects	
Baseline Demographic Characteristic	(N=156[a])	(N=152[a])
Gender		
Male	114 (73%)	95 (63%)
Female	42 (27%)	57 (27%)
Race		
Black	20 (13%)	15 (10%)
White	87 (56%)	94 (62%)
Other (primarily hispanic)	49 (31%)	43 (28%)
Weight (kg)		
males (mean)	77.1	79.6
females (mean)	68.9	67.9
Age (years)		
Mean	42.6	45.4
Minimum		
Maximum		
16-44	94 (60%)	78 (51%)
45-64	39 (25%)	45 (30%)
≥65	23 (15%)	29 (19%)
Diseases/Syndromes at Baseline[b]	(N=201[c])	(N=207[c])
COPD	13 (6%)	20 (10%)
Diabetes Mellitus	13 (6%)	14 (7%)
Hepatic Disease	7 (3%)	4 (2%)
Impaired Renal Function	6 (3%)	5 (2%)
Congestive Heart Failure	5 (2%)	7 (3%)

COPD = chronic obstructive pulmonary disease.
a Clinically evaluable subjects.
b Not all treated subjects were assessed for intercurrent disease/syndrome at study entry.
c Treated subjects.

Among the clinically evaluable study population, proportionally more males were studied in each arm. Otherwise, the two treatment arms appeared similar with regard to other demographic features.

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Summary of Baseline Risk Factors Associated with a Possible Unfavorable Outcome (Clinically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=156)		Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanic Acid (N=152)	
Risk Factors	Number and Percentage (%) of Subjects			
Subjects with at Least One Risk Factor*	109	(70%)	91	(60%)
APACHE score				
Mean	6.4		7.0	
Median				
Maximum				
Type of Infection				
Abscess only	69	(44%)	67	(44%)
Peritonitis only	60	(38%)	70	(46%)
Abscess and Peritonitis	27	(17%)	15	(10%)
Site of Infection				
Multiple	19	(12%)	18	(12%)
Underlying Disease				
Appendiceal rupture	81	(51%)	71	(47%)
Peptic ulcer perforation	32	(21%)	32	(21%)
Post/op abscess or perforation	32	(21%)	30	(20%)
Extreme Age				
>75	6	(4%)	12	(8%)
Health Insurance				
None	53	(34%)	47	(31%)

* ***italicized*** titles listed above represent "risk factors" (according to the applicant)

For the clinically-evaluable population, risk factors were similarly distributed between the two treatment groups at baseline with the exception of the infection type "abscess and peritonitis" being higher in the Trovan arm. (17% vs. 10%)

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Summary of Premature Discontinuations From Treatment (All-Treated Subjects)				
	Alatrofloxacin ↓ Trovafloxacin (N=201)		Imipenem/Cilastatin ↓ Amoxicillin/Clavulanac Acid (N=207)	
	Number and Percentage (%) of Subjects			
Total Discontinued	34	(17%)	37	(18%)
Discontinuations Related to Study Drug:	21	(10%)	14	(7%)
Adverse Event	13	(6%)	6	(3%)
Insufficient Response	7	(3%)	8	(4%)
Laboratory Abnormality	1	(<1%)	0	
Discontinuations Unrelated to Study Drug:	13	(6%)	23	(11%)
Adverse Event	5	(2%)	9	(4%)
Did Not Meet Randomization Criteria	1	(<1%)	1	(<1%)
Laboratory Abnormality	0		1	(<1%)
Lost to Follow-Up	0		2	(<1%)
Other	2	(<1%)	6	(3%)
Subject Died	3	(1%)	1	(<1%)
Protocol Violation	1	(<1%)	1	(<1%)
Withdrawn Consent	1	(<1%)	2	(<1%)

Reasons for premature discontinuation were comparable between study arms.

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Clinical Efficacy

Summary of Sponsor-Defined Clinical Response Rates at the End of Treatment and the End of Study (Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafloxacin (N=156)		Imipenem/Cilastatin ↓ Amoxicillin/Clavulanic Acid (N=152)		95% CI
	Number and Percentage (%) of Subjects				
End of Treatment:					
Number of Subjects Assessed	155	(100%)	142	(100%)	
Success (Cure + Improvement)	136	(88%)	122	(86%)	(-5.9, 9.5)
Distribution of Clinical Response:					
Cure	119	(77%)	104	(73%)	
Improvement	17	(11%)	18	(13%)	
Failure	19	(12%)	20	(14%)	
End of Study:					
Number of Subjects Assessed	156	(100%)	152	(100%)	
Success (Cure + Improvement)	129	(83%)	127	(84%)	(-9.2, 7.5)
Distribution of Clinical Response:					
Cure	128	(82%)	125	(82%)	
Improvement	1	(<1%)	2	(1%)	
Failure	27	(17%)	25	(16%)	

For the clinically-evaluable population, by the end of treatment and end of study visits, efficacy was similar between treatment arms. Similar results were seen for the clinical intent-to-treat population. (See next table.)

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A Summary of the Sponsor's-Assessment of Clinical Efficacy Results (Clinical Intent-to-Treat Subjects)				
	End of Treatment		End of Study	
	Alatrofloxacin ↓ Trovafloxacin (N=200)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid (N=199)	Alatrofloxacin ↓ Trovafloxacin (N=200)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid (N=199)
	Number and Percentage (%) of Subjects			
Number of Subjects Assessed	198 (100%)	193 (100%)	200 (100%)	199 (100%)
Success (Cure + improvement)	168 (85%)	163 (84%)	161 (81%)	162 (81%)
Distribution of Clinical Response:				
Cure	146 (74%)	136 (70%)	157 (79%)	156 (78%)
Improvement	22 (11%)	27 (14%)	4 (2%)	6 (3%)
Failure	30 (15%)	30 (16%)	39 (20%)	37 (19%)

According to the applicant, "Comparisons of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) supported equivalence of the two treatments in both the clinically evaluable and intent-to-treat analyses at the end of treatment (95% CI: -5.9%, 9.5% and -6.8%, 7.5%, respectively) and at the end of study (95% CI: -9.2%, 7.5% and -8.6%, 6.8%, respectively)."

Summary of Clinical Signs and Symptoms at Baseline, EOT, and EOS (Clinically Evaluable Subjects)						
	Alatrofloxacin ↓ Trovafloxacin			Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid		
	Baseline	EOT	EOS	Baseline	EOT	EOS
Sign/Symptom[a]	Percentage of Subjects With Clinical Signs and Symptoms					
Intra-abdominal Pain/Tenderness	92%	12%	7%	92%	16%	7%
Abdominal Rigidity	36%	0%	<1%	33%	0%	0%
Swelling	38%	2%	2%	46%	3%	<1%
Induration	11%	1%	<1%	9%	2%	2%
Surgical Wound Discharge	16%	16%	10%	13%	16%	10%
Mass	7%	0%	<1%	12%	1%	0%
Ileus	40%	<1%	<1%	39%	2%	0%
Hypotension	4%	1%	<1%	5%	<1%	0%
Leukocytosis	77%	16%	14%	74%	24%	13%
Bowel Sounds	55%	94%	94%	49%	95%	95%
Formed Bowel Movements	17%	75%	86%	16%	78%	85%
Flatulence	26%	76%	78%	24%	77%	84%
Intra-abdominal Pain/Tenderness	92%	14%	8%	91%	18%	8%
Abdominal Rigidity	34%	3%	<1%	32%	0%	<1%
Swelling	36%	5%	2%	41%	5%	2%
Induration	11%	2%	<1%	7%	2%	2%
Surgical Wound Discharge	16%	17%	10%	15%	17%	10%
Mass	8%	<1%	<1%	12%	2%	<1%
Ileus	37%	2%	<1%	38%	2%	0%
Hypotension	5%	4%	1%	5%	1%	0%
Leukocytosis	76%	18%	14%	74%	24%	13%
Bowel Sounds	56%	92%	94%	51%	94%	95%
Formed Bowel Movements	19%	71%	85%	15%	75%	83%
Flatulence	27%	75%	80%	24%	79%	83%

EOT=End of Treatment; EOS = End of Study
a Not all subjects were evaluated for all signs/symptoms at all timepoints.

For the clinically evaluable subjects, intra-abdominal signs and symptoms were comparable between populations at baseline, end of treatment, and end of study.

Other Indirect Measurements of Clinical Success (Clinical Intent-to-Treat Subjects)		
	Alatrofloxacin ↓ Trovafloxacin (n=200)	**Imipenem/Cilastatin ↓ Amoxicillin/Clavulanic Acid (n=199)**
Time to recovery (days)	(n=179) 7.9 ± 5.8*	(n=189) 8.2 ± 6.9*
Duration of post-op fever (days)	(n=199) 3.3 ± 3*	(n=197) 3.2 ± 3*
Duration of post-op hospitalization (days)	(n=193) 14.3 ± 14.5*	(n=195) 14.0 ± 14.2*
Median duration of hospitalization (days)	9	9

* = mean ± SD

As shown above, time to recovery, duration of post-op fever, duration of post-op hospitalization, and median duration of hospitalization was comparable between the two treatment arms.

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Microbiologic Efficacy:

Summary of Clinical Success (cure + improved) Rates at the End of Treatment and at the End of Study For the Most Frequently Isolated Baseline Pathogens[a]
(Clinically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=156)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanic Acid (N=152)	Alatrofloxacin ↓ Trovafloxacin (N=156)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanic Acid (N=152)
	Number of Subjects			
Pathogen	End of Treatment		End of Study	
Gram Positive Aerobes				
Alpha-haemolytic streptococci	9/12	4/4	8/12	6/6
Beta-hemolytic streptococci, Gp. B (= *S. agalactiae*)	0/1	1/1	0/1	0/1
S. viridans	18/20 (90%)	19/23 (83%)	18/20 (90%)	18/23 (78%)
S. anginosus	7/10	8/8	6/10	8/8
Streptococcus sp.	27/30 (90%)	38/41 (93%)	26/30 (87%)	40/43 (93%)
E. faecium	3/4	5/6	3/4	5/6
E. faecalis	7/13	12/16 (75%)	6/13	12/17 (71%)
Enterococcus sp.	7/10	13/18 (72%)	7/10	15/20 (75%)
S. aureus	8/11	1/3	8/11	1/3
Gram Negative Aerobes				
E. coli	72/77 (94%)	52/58 (90%)	66/77 (86%)	51/59 (86%)
E. aerogenes.	3/3	2/2	3/3	2/2
E. cloacae	6/7	5/7	5/7	6/7
Enterobacter sp.	2/3	1/1	2/3	1/1
K. pneumoniae	12/15 (80%)	10/14	10/15 (67%)	10/14
P. aeruginosa	15/16 (94%)	14/17 (82%)	14/16 (88%)	15/18 (83%)
Gram Positive Anaerobes				
Peptostreptococcus sp.	12/14	7/8	11/14	6/8
Clostridium sp.	4/5	8/9	4/5	9/10
Corynebacterium sp.	3/3	5/5	3/3	6/6
Gram Negative Anaerobes				
Prevotella buccae	1/2	1/2	1/2	1/2
Prevotella intermedia	1/1	0	1/1	0/0
Prevotella sp.	10/13	2/4	10/13	3/5
B. fragilis	30/31 (97%)	28/34 (82%)	26/31 (84%)	27/36 (75%)
B. thetaiotaomicron	14/18 (78%)	13/13	11/18 (61%)	12/13
B. uniformis	7/7	9/10	5/7	9/10
B. vulgatus	5/7	7/7	5/7	7/7
Bacteroides sp.	7/9	11/12	7/9	11/13
F. necrophorum	3/3	2/2	3/3	2/2
F. nucleatum	1/2	1/1	1/2	1/1
Fusobacterium sp.	6/7	2/2	6/7	2/2

a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

Comparable bacteriologic efficacy (often presumptively determined based on clinical response) was observed in both treatment arms for the majority of pathogens isolated at the time of the defining surgery. However, TROVAN appeared (albeit small numbers) to have lower efficacy against *B. thetaiotaomicron* compared to the control arm. (11/18 vs. 12/13)

For those patients who received repeat cultures at follow up, the development of resistance to trovafloxacin was not seen.

Safety

Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Alatrofloxacin ↓ Trovafloxacin (N=201)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid (N=207)
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	128/201 (64%)	120/207 (58%)
Treatment-Related Adverse Events	29/201 (14%)	23/207 (11%)
Discontinuations from Treatment Due to an Adverse Event: All Causality	19/201 (9%)	19/207 (9%)
Discontinuations Due to a Treatment-Related Adverse Event	13/201 (6%)	6/207 (3%)
Clinically Significant Laboratory Abnormalities	142/198 (72%)	153/205 (75%)
Deaths*	11	11
Deaths during study period (entry → 30 days post-therapy)	7	5

Adverse event reporting (all causality and treatment-related) was similar between the two treatment groups.

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Deaths

Eleven (11) deaths were reported for both treatment groups. Seven and five patients, respectively, died during the study period (entry to 30 days post-therapy). Narrative summaries for these 12 patients are provided below.

Four subjects in the TROVAN group (Subjects 5525-0068, 5533-0110, 6256-0404 and 6524-0918) and two subjects in the comparator regimen (Subjects 5533-0086, and 6052-0806) died while receiving therapy. None of these deaths were considered by the investigator to be related to study drug.

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NARRATIVES OF ALL REPORTED DEATHS
(On Therapy or Within 30 days Posttherapy)

Phase II/III Studies - Complicated intra-abdominal infection

Alatrofloxacin/Trovafloxacin

Subject 154-124-5525-0068	This 63-year old white male underwent radiation therapy for treatment of anal carcinoma. He was admitted to a center in the US for surgical repair and treatment of radiation therapy-associated perforation of the small bowel with abscess formation. His previous medical history was significant for anal carcinoma and hypertension. The subject was maintained on erythropoietin for the treatment of underlying anemia at the time of hospital admission. The subject was treated successfully with a 7-day course of 300 mg alatrofloxacin daily. His clinical course improved and he was transferred on day 4 from the surgical intensive care unit (SICU). On day 6, his condition rapidly deteriorated following a cardiopulmonary/pulmonary arrest due to mucous plugging and anoxia, and he was transferred back to the SICU. The patient expired on day 8 secondary to complications resulting from the cardiopulmonary/pulmonary arrest.
Subject 154-124-5533-0110	This 79-year old white male presented to the Emergency Department at a center in the US with acute lower quadrant pain, low grade fever, and multiple episodes of nausea. The subject was found surgically to have an acute appendicitis with an inflamed terminal ileum and cecum requiring resection. He was randomized into study on day 1 and treated for 11 days with intravenous alatrofloxacin 300 mg daily; one dose was missed. No chronic medications were listed at screening nor was his previous medical history significant for cardiac disease. The subject suffered a cardiac arrest on day 7 which was considered to be due to a pulmonary embolism. The subject continued to deteriorate and multiple organ failure was diagnosed on day 10. The subject was made "do not resuscitate" on post-operative day 11, the family requested all medication to be discontinued including study drugs, life support was withdrawn, and the patient expired on the same day.
Subject 154-124-6151-0603	This 77-year old white female with a 6-month history of abdominal pain and 3-month progressive weight loss (15 lb.) underwent a left and sigmoid colectomy for perforated sigmoid colon with fecal peritonitis at a center in the US. Previous medical history was significant for angina, constipation, COPD, and peptic ulcer disease. She was treated with alatrofloxacin 300 mg IV daily for 4 days. Her hospital course was complicated by thrombocytopenia which was thought to be related to study drug, recurrent pleural effusions (starting on day 3) and hemorrhage from the right chest tube (day 22) secondary to diffuse metastatic lung carcinoma, and acute renal failure on day 21. The subject expired on day 23 from cardiorespiratory arrest secondary to chronic obstructive pulmonary disease, lung carcinoma, and coronary disease.
Subject 154-124-6256-0404	This 68-year old white male underwent a sigmoid colectomy and Hartmann's closure of the rectal stump for peritonitis resulting from a nontraumatic perforation of the sigmoid colon at a center in the UK. Previous medical history was not significant for any underlying diseases nor was the subject maintained on chronic therapy. However, his prognosis was poor with a baseline APACHE II score of 27. The subject was treated with alatrofloxacin 300 mg IV daily for 3 days. The subject experienced multiple organ failure secondary to the disease under study and expired on post-operative day 3.

NARRATIVES OF ALL REPORTED DEATHS
(On Therapy or Within 30 days Posttherapy)

Phase II/III Studies - Complicated intra-abdominal infection

Subject 154-124-6451-0721	This 64-year old white female with peritonitis underwent surgical repair of perforated small bowel felt secondary to amyloidosis at a center in Canada. Concurrent active medical conditions included COPD, congestive heart failure, angina, and hepatic disease. The subject was maintained on cardiac drugs at time of hospital admission. She was randomized into study and received 8 days of intravenous alatrofloxacin 300 mg daily. The subject experienced severe restrictive cardiomyopathy, amyloidosis, and acute pulmonary decompensation on day 3. Her clinical course further deteriorated and on day 14, she had a cardiac arrest that was considered secondary to the COPD, restrictive cardiomyopathy, congestive heart failure, and amyloidosis. She subsequently lapsed into unconsciousness and expired on the same day.
Subject 154-124-6518-0934	This 72-year old white male underwent surgery for a perforated gastric ulcer at a center in Poland. Two weeks post-operatively, the subject underwent further surgery for peritonitis and drainage of multiple abscesses related to an anastomotic leakage from the prior surgery. He was subsequently randomized into study and received 14 days of alatrofloxacin 300 mg IV daily. The subject was maintained on multiple concomitant medications, including gastrointestinal agents, blood transfusions, anticoagulants, cardiac drugs, and an antifungal agent (fluconazole). His clinical course improved until day 11 when signs and symptoms of peritonitis were again noted. Surgical cleaning of the wound was performed on day 14 and no further antibiotics were administered. The subject expired on day 20 of multiple organ failure due to the disease under study. Autopsy findings included anastomotic healing, fibrocaseous peritonitis, nephritis, partial necrosis of tissue surrounding the pancreas, advanced cerebral and peripheral atherosclerosis, and lung venostasis.
Subject 154-124-6524-0918	This 68-year old white female with peritonitis secondary to bowel perforation from rectal carcinoma underwent a Hartmann's procedure at a center in Poland. The subject was treated with alatrofloxacin 300 mg daily IV for 7 days. Previous medical history was significant for COPD, congestive heart failure, and ischemic heart disease which were maintained with respiratory and cardiac drugs. Prognosis was poor and the subject expired on day 7 due to multisystem failure.

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Comparator

Subject 154-124-5533-0086	This 72-year old Hispanic female had motor vehicle accident-related multisystem trauma with upper extremity fractures, ileal perforation, and evolving sepsis. The ileal perforation was surgically repaired at a center in the US. She was treated with imipenem/cilastatin 1000 mg IV every 8 hours for 10 days. She had no significant previous medical history nor maintained on chronic drug therapy prior to hospitalization. During her hospital stay, she received concomitant medications consistent with the disease under study and the associated surgical procedure. Chest x-rays confirmed adult respiratory distress syndrome caused by evolving sepsis on day 6 and the subject continued on respiratory support throughout her hospitalization. Her clinical course worsened on day 9 with evidence of an abdominal site infection and sepsis; the antibiotic therapy was switched to ampicillin/sulbactam and metronidazole on day 10. She expired on day 13 due to complications associated with the motor vehicle accident.
Subject 154-124-5553-0695	This 64-year old white male underwent drainage of a retroperitoneal abscess which developed from a previous enterolysis for small bowel obstruction at a center in the US. Previous medical history was significant for COPD, asthma, bladder and prostate cancer, and metastatic carcinoma of the right lung and left retroperitoneum. His pre- and post-operative course was complicated by cardiac arrhythmias (supraventricular tachycardia, atrial flutter with atrioventricular block). He also had a proximal femoral vein deep venous thrombosis pre-randomization. He was treated with imipenem/cilastatin 1000 mg every 8 hours for 8 days. His clinical course deteriorated, the subject was ventilator-dependent, and he was hemodynamically stabilized on dopamine and hyperalimentation. Due to his deteriorating neurologic status and end-stage condition, all supportive measures were withdrawn on day 14. The subject expired due to cardiac arrest on day 17.
Subject 154-124-6018-0497	This 82-year old white male was hospitalized for digestive hemorrhage due to hiatal hernia at a center in France. He underwent a vagotomy with pyloroplasty and then developed post-operative acute respiratory failure. He subsequently developed peritonitis secondary to the previous abdominal surgery and was randomized into study. His APACHE II score at baseline was 32. He was treated with imipenem/cilastatin 500 mg IV every 6-8 hours for 14 days. His previous medical history was significant for COPD, coronary insufficiency, transient ischemic accidents, renal impairment, and an abdominal aortic aneurysm. His clinical course deteriorated with multiple surgeries for acute cholecystitis, fistulization of the pyloroplasty, and evisceration of the surgical abdominal wound. The subject developed worsening respiratory failure, renal failure, and cardiac failure, and expired on day 26 due to multisystem organ failure.
Subject 154-124-6052-0806	This 86-year old white male underwent appendectomy for a perforated appendix with diffuse peritonitis at a center in the US. Previous medical history was significant for stroke, hypertension, and urinary tract infection. The subject was treated with imipenem/cilastatin 250 mg every 6 hours for 13 days; one dose was missed on day 3. He was diagnosed with aspiration pneumonitis by chest x-ray on day 1 following surgery. On day 5, there was evidence of a new cerebrovascular accident confirmed clinically by seizure-like activity. The subject expired on day 13 due to the recurrent stroke.

Subject 154-124-6441-0525

This 79-year old white male underwent surgical repair of a perforated duodenal ulcer at a center in France. Previous medical history was significant for impaired renal function and an adrenal gland tumor which was diagnosed at time of randomization. The subject was treated with imipenem/cilastatin 1000 mg IV every 12 hours for 2 days, then 500 mg IV every 12 hours for 1 day, then 500 mg IV every 8 hours for 11 days. Abdominal cultures were positive for *Candida albicans* at baseline, and on days 3, 6, and 11; blood cultures were positive for *Candida albicans* on days 9, 10, 12 and 19. The subject was treated with fluconazole and amphotericin B. On day 19, his clinical course deteriorated and the subject was intubated for adult respiratory distress syndrome. The subject expired on day 23 from Candida septicemia and disease under study.

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9. Conclusions:

Compared to Primaxin → Augmentin (an adequate comparator), the MO believes Pfizer has shown TROVAN to be safe and effective in the treatment of complicated intra-abdominal infections due to numerous pathogens.

In their proposed labeling, Pfizer requests the following be included in the INDICATIONS AND USAGE section:

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DRAFT LABELING

[redacted]

As discussed in the 1992 DAIDP Points-to-Consider document, to include an organism in a treatment indication, the following criteria are recommended:

1. the organism is generally considered pathogenic AND
2. the organism represents at least 10% of the evaluable cases OR
3. the organism represents 10 total (whichever is higher) AND
4. the eradication rate must be clinically acceptable.

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The PTC document goes on to discuss how one might include a pathogen in labeling where <10% of cases were associated with the "pathogen":

1. generally accepted to be a pathogen at the site of infection
2. in vitro activity is at least similar to that of other pathogens more substantially evaluated in clinical trials
3. the mechanism of resistance is similar to that of other pathogens more substantially evaluated in clinical trials

4. no scientific data exist suggesting differences in the management of infections due to these pathogens

Although not discussed in the PTC document, the following caveats should be considered in the approval of pathogens for treatment indications:

1. If this is the first time a pathogen is to be included in the INDICATIONS AND USAGE section of product labeling (i.e., no other label is approved for this pathogen), perhaps a higher standard of evidence may be appropriate.
2. All pathogens *should* be fully speciated for each treatment indication in the INDICATIONS AND USAGE section with the exception of viridans group streptococci and *Peptostreptococcus spp.* (e.g., *Bacteroides spp.* would be unacceptable because *in vitro* susceptibility can vary significantly between species of bacteroides within the genus).
3. It's feasible to use pathogen data from other treatment indications to support efficacy in the treatment indication under study as long as that extrapolation is appropriate and reasonable (clinically and pharmacodynamically). For example, anaerobes for complicated intra-abdominal infection and GYN infections could be combined in inferring a drug's *in vivo* efficacy against pathogens included in approved product labeling. However, for example, the extrapolation of *E. coli* efficacy from UTI studies to intra-abdominal infections would <u>not</u> be appropriate. (NOTE: Severity of treatment indication as well as dose and duration should be considered in making this extrapolation from one treatment indication to another.)

   MO Comment : The MO does not believe that GYN/Pelvic infection efficacy data can be extrapolated to support the CIAI indication, because CIAI patients are often sicker (e.g., mortality is not rare in CIAI; it is rare in GYN/Pelvic infections).

The MO believes Pfizer has presented substantial evidence supporting approval for the following pathogens:

Escherichia coli, Bacteroides fragilis, Streptococcus viridans, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus faecalis, Peptostreptococcus spp., and *Prevotella spp.*

> ***MO Comment :*** Following discussion with the reviewing microbiologist, "viridans group streptococci" is the preferred collective name for *S. viridans* including other streptococci. e.g., *Streptococcus anginosus,*)
>
> ***MO Comment :*** Following review of the NDA, the MO could not find convincing *in vitro* or clinical data suggesting that different prevotella species demonstrate variable susceptibility patterns or clinical outcomes to TROVAN. Therefore, the MO recommends approval of "*Prevotella* species" for this treatment indication.

The MO does not believe the following bacteria should be included in this treatment indication:

Bacteroides thetaiotaomicron : As noted previously, efficacy appears to be lower for this pathogen (relative to the comparator regimen) in the clinical study AND *in vitro* data show the MIC_{90} for trovafloxacin to be high: 1.5 mcg/mL. Therefore, *in vitro* susceptibility testing support this clinical concern.

Staphylococcus aureus : Following the above discussion, there were 135 bacteriologically-evaluable TROVAN recipients. Ten percent of 135 is 14. Only 11 *S. aureus* were isolated. This number does not meet the points-to-consider guidance.

As already discussed above, the Agency has been reluctant to include genus information alone (without speciation) in the INDICATIONS AND USAGE section of product labeling, because susceptibility testing may differ for species within a genus. Therefore, unlike prevotella, the MO recommends the following unspeciated pathogens/organisms **not** be included in product labeling:

Enterobacter species, *Enterococcus* species, *Corynebacterium* species, *Fusobacterium* species, *Streptococcus* species or *Bacteroides* species.

Unfortunately, the applicant did not speciate these organisms during the trial and this information cannot be inferred.

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10. Recommendations:

DRAFT LABELING

[redacted]

In addition, the following should be included in the CLINICAL STUDIES section:

DRAFT LABELING

[redacted]

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/S/

Brad Leissa, MD
Medical Officer/HFD-590

cc: Orig. NDA
Division file
HFD-590/MO/Leissa
HFD-590/MO/Alivisatos
HFD-590/MO/Cox
HFD-590/CSO/Kimzey

Concurrence only: DivDir/Goldberger

/S/ 11/4/9

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Medical Officer's Review of NDAs 20-759 and 20-760

Surgical Prophylaxis

1.1 NDAs : 20-759 (oral tablets) and 20-760 (injection)

1.2 Applicant identification
- 1.2.1 Pfizer Central Research
- 1.2.2 Address and telephone number:
  Eastern Point Road
  Groton, CT 06340

APPEARS THIS WAY ON ORIGINAL

1.3 Submission/review dates
- 1.3.1 Date of submission : 27 December 1996
- 1.3.2 CDER stamp date : 30 December 1996
- 1.3.3 Date submission received by reviewer : 6 January 1997
- 1.3.4 Date review begun : 4 June 1998
- 1.3.5 Date review completed : 12 December 1997

1.4 Drug identification
- 1.4.1 Generic name : trovafloxacin mesylate (tablets)
  alatrofloxacin mesylate (solution for injection)
- 1.4.2 Proposed trade name : **TROVAN™**
- 1.4.3 Other names used during development: CP-99,219 (tablet)
  CP-116,517 (IV)

1.5 Pharmacologic Category : fluoronaphthyridone

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1.6 Dosage form : See 1.1 above

1.7 Route of Administration : intravenous (20-760) and oral (20-759)

1.8 Proposed Indication & Usage section :

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SURGICAL PROPHYLAXIS - PROPHYLAXIS OF INFECTION ASSOCIATED WITH ELECTIVE SURGICAL PROCEDURES, where there is increased risk of postoperative infections (e.g., colorectal surgery, vaginal and abdominal hysterectomy).

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1.9 Proposed Dosage and Administration section :

1.10 Related Drugs : See 1.4.3 above.

1.11 Material Reviewed : NDAs and amendments

1.12 Regulatory Background

A) Anti-Infective Drug Products Approved For This Indication

(1) The following drugs are specifically approved for "surgical prophylaxis":

CEFTRIAXONE (Rocephin)

SURGICAL PROPHYLAXIS: The preoperative administration of a single 1 gm dose of Rocephin may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as **contaminated or potentially contaminated** (eg, vaginal or abdominal hysterectomy or cholecystectomy for chronic calculous cholecystitis in high-risk patients, such as those over 70 years of age, with acute cholecystitis not requiring therapeutic antimicrobials, obstructive jaundice or common duct bile stones) and in surgical patients for whom infection at the operative site would present serious risk (eg, during coronary artery bypass surgery). Although Rocephin has been shown to have been as effective as cefazolin in the **prevention of infection following coronary artery bypass surgery**, no placebo-controlled

trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery.

When administered prior to surgical procedures for which it is indicated, a single 1 gm dose of Rocephin provides protection from most infections due to susceptible organisms throughout the course of the procedure.

Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

DOSAGE AND ADMINISTRATION:

For preoperative use (surgical prophylaxis), a single dose of 1 gram administered intravenously 1/2 to 2 hours before surgery is recommended.

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CEFONICID

SURGICAL PROPHYLAXIS : Administration of a single 1 gram dose of Monocid before surgery may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as **contaminated or potentially contaminated** (e.g., colorectal surgery, vaginal hysterectomy, or cholecystectomy in high-risk patients), or in patients in whom infection at the operative site would present a serious risk (e.g., prosthetic arthroplasty, open heart surgery). Although cefonicid has been shown to be as effective as cefazolin in **prevention of infection following coronary artery bypass surgery**, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery or prosthetic heart valve replacement.

DOSAGE AND ADMINISTRATION:

When administered 1 hour prior to appropriate surgical procedures (see INDICATIONS AND USAGE), a 1 gram dose of Monocid provides protection from most infections due to susceptible organisms throughout the course of the procedure. Intraoperative and/or postoperative administrations of Monocid are not necessary. Daily doses of Monocid may be administered for 2 additional days in patients undergoing prosthetic arthroplasty or open heart surgery.

(2) Other drugs labeled for "pre-" or "peri-operative" prophylaxis:

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CEFUROXIME (Zinacef, Cefurox)

PREVENTION: The preoperative prophylactic administration of ZINACEF may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified as **clean-contaminated or potentially contaminated** procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. ZINACEF should usually be given one-half to 1 hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

DOSAGE AND ADMINISTRATION:

For preventive use for clean-contaminated or potentially contaminated surgical

procedures, a 1.5-gram dose administered intravenously just before surgery (approximately one-half to 1 hour before the initial incision) is recommended. Thereafter, give 750 mg intravenously or intramuscularly every 8 hours when the procedure is prolonged. For preventive use during open heart surgery, a 1.5-gram dose administered intravenously at the induction of anesthesia and every 12 hours thereafter for a total of 6 grams is recommended.

CEFOTAXIME (Claforan)

The administration of Claforan(R) preoperatively reduces the incidence of certain infections in patients undergoing surgical procedures (e.g., abdominal or vaginal hysterectomy, gastrointestinal and genitourinary tract surgery) that may be classified as **contaminated or potentially contaminated**.

DOSAGE AND ADMINISTRATION:

To prevent postoperative infection in contaminated or potentially contaminated surgery, the recommended dose is a single 1 gram IM or IV administered 30 to 90 minutes prior to start of surgery.

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CEFAZOLIN (Ancef, Kefzol)

Perioperative Prophylaxis : The prophylactic administration of Kefzol preoperatively, intraoperatively, and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as **contaminated or potentially contaminated** (eg, vaginal hysterectomy or cholecystectomy in high-risk patients such as those over 70 years of age who have acute cholecystitis, obstructive jaundice, or common-bile-duct stones).

The prophylactic administration of Kefzol should usually be discontinued within a 24-hour period after the surgical procedure. For surgery in which the occurrence of infection may be particularly devastating (eg, **open-heart surgery and prosthetic arthroplasty**), the prophylactic administration of Kefzol may be continued for 3 to 5 days following the completion of surgery. If there are signs of infection, specimens for culture should be obtained for the identification of the causative organism so that appropriate therapy may be instituted (See DOSAGE AND ADMINISTRATION).

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DOSAGE AND ADMINISTRATION:

To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended doses are:

a) 1 gram I.V. or I.M. administered 1/2 hour to 1 hour prior to the start of surgery.
b) For lengthy operative procedures (e.g., 2 hours or more), 500 mg to 1 gram I.V. or I.M. during surgery (administration modified depending on the duration of the operative procedure).
c) 500 mg to 1 gram I.V. or I.M. every 6 to 8 hours for 24 hours postoperatively.

It is important that (1) the preoperative dose be given just (1/2 to 1 hour) prior to the start of surgery so that adequate antibiotic levels are present in the serum and tissues at the time of initial surgical incision; and (2) Ancef be
administered, if necessary, at appropriate intervals during surgery to provide sufficient levels of the antibiotic at the anticipated moments of greatest exposure to infective organisms.

In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Ancef (sterile cefazolin sodium) may be continued for 3 to 5 days following the completion of surgery.

CEFAMANDOLE (Mandol)

Preventive Therapy : The administration of Mandol preoperatively, intraoperatively, and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as **contaminated or potentially contaminated** (eg, gastrointestinal surgery, cesarean section, vaginal hysterectomy, or cholecystectomy in high-risk patients such as those with acute cholecystitis, obstructive jaundice, or common-bile-duct stones).

If signs of infection occur, specimens for culture should be obtained for identification of the causative organism so that appropriate antibiotic therapy may be instituted.

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DOSAGE AND ADMINISTRATION:

For perioperative use of Mandol, the following dosages (for adults) are recommended: 1 or 2 g intravenously or intramuscularly 1/2 to 1 hour prior to the surgical incision followed by 1 or 2 g every 6 hours for 24 to 48 hours.

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MEZLOCILLIN (Mezlin)

PREVENTION : The administration of MEZLIN(R) perioperatively (preoperatively, intraoperatively, and postoperatively) may reduce the incidence of infections in patients undergoing surgical procedures (e.g. vaginal hysterectomy and colorectal surgery) that may be classified as **contaminated or potentially contaminated**. Effective perioperative use for surgery depends on the time of administration. To achieve effective tissue levels, MEZLIN(R) should be given 1/2 hour to 1 1/2 hours before surgery.

For patients undergoing colorectal surgery, **preoperative bowel preparation by mechanical cleansing as well** as with a non-absorbable antibiotic (e.g. neomycin) is recommended.

If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapy may be instituted.

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DOSAGE AND ADMINISTRATION:

To prevent postoperative infection in contaminated or potentially contaminated surgery, the following doses are recommended: 4g IV given 1/2 hour to 1 1/2 hours prior to the start of surgery. 4g IV given 6 hours and 12 hours later.

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METRONIDAZOLE (Flagyl)

PROPHYLAXIS : The prophylactic administration of Flagyl I.V. or Flagyl I.V. RTU preoperatively, intra-operatively, and post-operatively may reduce the incidence of postoperative infection in patients undergoing elective **colorectal surgery which is classified as contaminated or potentially contaminated**.

Prophylactic use of Flagyl I.V. or Flagyl I.V. RTU should be discontinued within 12 hours after surgery.

If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism(s) so that appropriate therapy may be given (see Dosage And Administration).

DOSAGE AND ADMINISTRATION:

For surgical prophylactic use, to prevent postoperative infection in contaminated or potentially contaminated colorectal surgery, the recommended dosage schedule for adults is:

a) 15 mg/kg infused over 30 to 60 minutes and completed approximately one hour before surgery; followed by
b) 7.5 mg/kg infused over 30 to 60 minutes at 6 and 12 hours after the initial dose.

It is important that (1) administration of the initial preoperative dose be completed approximately one hour before surgery so that adequate drug levels are present in the serum and tissues at the time of initial incision, and (2) Flagyl I.V. or Flagyl I.V. RTU be administered, if necessary, at 6-hour intervals to maintain effective drug levels. Prophylactic use of Flagyl I.V. or Flagyl I.V. RTU should be limited to the day of surgery only, following the above guidelines.

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CEFOTETAN (Cefotan)

The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as **clean contaminated or potentially contaminated** (e.g., cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery). If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

DOSAGE AND ADMINISTRATION:

To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery.

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CEFOXITIN (Mefoxin)

indicated for the prophylaxis of infection in patients undergoing uncontaminated **gastrointestinal surgery, vaginal hysterectomy, abdominal hysterectomy, or cesarean section**. If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate treatment may be instituted.

Effective prophylactic use depends on the time of administration. MEFOXIN usually should be given one-half to one hour before the operation, which is sufficient time to achieve effective levels in the wound during the procedure. Prophylactic administration should usually be stopped within 24 hours since continuing administration of any antibiotic increases the possibility of adverse reactions but, in the majority of surgical procedures, does not reduce the incidence of subsequent infection.

DOSAGE AND ADMINISTRATION:

For prophylactic use in uncontaminated gastrointestinal surgery, vaginal hysterectomy, or abdominal hysterectomy, the following doses (for adults) are recommended:

2 grams administered intravenously just prior to surgery (approximately one-half to one hour before the initial incision) followed by 2 grams every 6 hours after the first dose for no more than 24 hours.

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B) Regulatory Guidance

1992 DAIDP "Points to Consider" document (PTC)

No guidance is provided in the PTC for this indication.

IDSA/FDA Guidelines (*Clinical Infectious Diseases*; 15, Suppl. 1; Nov. 1992)

The IDSA/FDA Guidelines discuss colorectal surgical prophylaxis but do not discuss hysterectomy surgical prophylaxis.

The guidelines distinguish between the prophylactic (within 12 hours of surgery) versus treatment (>12 hours from the time of surgery after the development of signs of serious infection, such as septic shock, abscess formation, or diffuse peritonitis) use of an anti-infective drug product.

Three different surgical conditions exist when one considers the need for anti-infective prophylaxis:

1. "contaminated or dirty" operations : gun-shot wound, perforation of the gastrointestinal tract (ruptured appendix, perforated divertuculum)

2. "clean-contaminated" operations : vaginal hysterectomy and colorectal operations

3. "clean" operations where prophylaxis is not justified : mastectomy, inguinal hernia repair

Prophylaxis is indicated for "dirty/contaminated" and "clean-contaminated" (colorectal & hysterectomy) procedures, but NOT "clean" (e.g., hernia repair) except where vascular grafts and prosthetic devices are present.

According to the guidance, an anti-infective drug product under development for surgical prophylaxis should meet the following objectives:

- prevent postoperative infectious morbidity and mortality;
- reduce the length and cost of hospital care;
- be the cause of minimal side effects (e.g., cause minimal *C. difficile* colonization leading to antibiotic-associated diarrhea & pseudomembranous colitis);
- give rise to minimal adverse effects on the microbial flora of the patient or hospital. (e.g., the promotion of antimicrobial resistance)

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Furthermore, the Guidelines continue, in addition to a product achieving the above objectives, an anti-infective drug should be:

- active against the pathogens most likely to contaminate the wound;
- given in appropriate doses, and at a time that ensures adequate concentrations at the incision site during the potential contamination;
- safe; and
- administered for the shortest effective period in order to minimize cost and adverse drug effects.

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General Surgical Prophylaxis Points Discussed in the Guideline:

- Additional measures to reduce infection such as pre-operative skin antisepsis, wound irrigation (preferably without antibiotics), prophylactic drainage, or variations in surgical technique should be clearly identified in the protocol, should be standardized insofar as possible, and should be recorded in the course of the study.

- In general, the first dose of a parenterally-administered antibiotic should be selected to achieve peak target concentrations in the primary surgical site at the time of the initial incision.

- Although not required for evaluability, it is highly desirable to record antimicrobial resistance patterns of infecting pathogens in both treatment and control groups in order to analyze for evidence of "emergence" of resistance.

- Duration of follow-up should be clearly defined and appropriate to the surgical procedure. Ordinarily, a 4-week follow-up is sufficient.

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Specific Colorectal Surgical Prophylaxis Points Discussed in the Guideline:

Approximately 43% of patients on a placebo treatment arm developed post-operative wound infections (vs. in the active-control, oral treatment group). Subsequent studies have identified wound infection rates of when an oral antimicrobial bowel preparation, such as neomycin, was used. When single-dose cefotetan prophylaxis was studied, the infection rate was 14% compared with 11% for cefoxitin q6h. Therefore, the IDSA authors for this chapter express their concern that parenteral cephalosporin prophylaxis may be less (>9% infection rate) effective than oral antimicrobial bowel preparation .

> ***MO Comment :*** The IDSA guidelines express concern that cephalosporin may not be the best comparator agents where clinical trials are designed to assess the activity of a new anti-infective drug product in preventing post-operative surgical infections.

Risk factors for postoperative infection in colorectal operations include the following:

- Rectal resections (abdominal-perineal resections) are associated with higher rates of infection than intra-peritoneal resections.
- Operations lasting more than 3½ or 4 hours are associated with more infections than those of shorter duration.
- Inadequate bowel preparation (e.g., isotonic lavage solution)
- Emergency surgical procedures

APPEARS THIS WAY ON ORIGINAL

Failure of Prophylaxis (as defined in the IDSA/FDA Guidelines):

- Postoperative infection within the primary operative incision and/or the peritoneal cavity, including peritonitis and abscess formation.
  - Infection developing in the **primary operative incision(s)** should be classified as failure of antimicrobial prophylaxis.
  - Infection developing in a **distant site** (e.g., urinary tract, respiratory tract, IV catheter, etc.) should be reported but not included as a criterion of success or failure of prophylaxis.
- Any unexplained use of anti-infective agents in the 4-week period following the primary operation.
- Any drainage procedure at the operative site or in and around the peritoneal cavity for infection.
- The development of an anastomotic leak.

APPEARS THIS WAY ON ORIGINAL

The Guidelines note, "A minimum of 50 evaluable patients per participating site center is required."

APPEARS THIS WAY ON ORIGINAL

2. Table of Contents: not applicable

3. Chemistry/Manufacturing Controls: See chemist's review.

4. Animal Pharmacology/Toxicology: See pharmacologist's review.

5. Microbiology: See microbiologist's review.

APPEARS THIS WAY ON ORIGINAL

6. Human Pharmacokinetics/Pharmacodynamics: See biopharm review.

The peak blood level (C_{max}) of alatrofloxacin at the 300 mg intravenous dose (trovafloxacin equivalent dose) used for intra-abdominal infections is 4.4 μg/mL with a half-life of 10.8 hours. The fluid/serum concentration ratio of trovafloxacin in peritoneal fluid after IV administration of 200 mg alatrofloxacin was 0.39. Mean tissue/serum concentration ratios for gynecologic tissues (ovary, uterus, myometrium, cervix and fallopian tubes) after single or multiple doses of oral trovafloxacin 200 mg. Thus, based upon its pharmacokinetic profile, single daily intravenous doses of

300 mg alatrofloxacin will exceed the MIC_{90} values of pathogens commonly involved in intra-abdominal and acute pelvic infections.

MO Comment : The applicant requests approval of the 200 mg dose.

7. Human Clinical Experience: not applicable

APPEARS THIS WAY
ON ORIGINAL

8. Clinical Studies:

Summary of the two studies (significant differences between the two studies are highlighted in bold lettering):

	STUDY 154-128	**STUDY 154-146**
	Colorectal	**Hysterectomy (abdominal & vaginal)**
Study design	Randomized, double-blind, double-dummy, comparative, multicenter	same
Study dates	April 1995 - March 1996	January - June 1996
Gender/age	Males/females; ≥18 yo	Females; ≥18 yo
Location	US, Canada	US
Trovan dosing (NOTE: T_{max} of PO = 1-2 hrs T_{max} of IV = end of 60' infusion)	200 mg **IV within 2 hours of surgery and infused over 1 hour**	200 mg **PO** trovafloxacin was given **30-60 mins. prior to surgery**
Comparator	2g **cefotetan** IV was given 30-60 mins. prior to surgery and infused over 3-5 minutes	2g **cefoxitin** IV was administered up to 30 minutes prior to the surgery (and to be infused over 5-15 minutes). Cefoxitin could be given as a 2nd dose if the surgical procedure lasted >4 hrs OR there was >1500 mL of blood loss)
Target enrollment	TROVAN = 200 CEFOTAN = 200	TROVAN = 175 MEFOXIN = 175
Target evaluability	not specified	TROVAN = 143 MEFOXIN = 143
How many received prophylaxis?	TROVAN = 256 CEFOTAN = 236	TROVAN = 188 MEFOXIN = 175
Visits	• Pre-surgery (-48h) • Once daily while hospitalized • Days 28-35 of study	• Pre-surgery (-72h) • Once daily while hospitalized • Days 24-36 of study
Primary efficacy parameter	Incidence of primary site infections at EOS, including: • Surgical site infection • Intraabdominal infection • Bacteremia (if no "distant site") • Unexplained fever	Incidence of primary site infections at EOS, including: • Surgical site infection • Pelvic cellulitis • Pelvic abscess • Infected pelvic hematoma
Secondary efficacy parameters	Distant site infections (e.g., pneumonia, UTI, IV catheter infection, etc.) NOTE: Could include bacteremia if not believed related to the colorectal procedure	Distant site infections (e.g., pneumonia, UTI, IV catheter infection, etc.)
Inclusion criteria	• Elective surgery of colon/rectum • Time to complete preoperative bowel preparation (GoLYTELY)	Elective abdominal or vaginal hysterectomies for non-malignant disease processes (e.g., dysplasia, abnormal bleeding, uterine prolapse, leiomyomas)

APPEARS THIS WAY
ON ORIGINAL

Exclusion criteria APPEARS THIS WAY ON ORIGINAL	• Emergency colorectal operations • Decompensated intestinal obstruction • Active inflammatory bowel disease involving the colon • Revision of a previous operation that has involved large bowel resection (e.g. revision of a colostomy and ileorectal anastomosis). • Subjects with a bacterial infection at the time of surgery or who were administered an antibiotic within 1 week prior to surgery.	• Emergency hysterectomy • Hysterectomy for malignancy • Outpatient surgical hysterectomy • Subjects with a bacterial infection at the time of surgery or who were administered an antibiotic within 1 week prior to surgery. APPEARS THIS WAY ON ORIGINAL
Definition of failure APPEARS THIS WAY ON ORIGINAL	• Development of infection in the primary operative incision(s). • Development of an unexplained fever requiring systemic antibiotic intervention. • Use of any systemic anti-infective drug during the 30-day post-operative period for treatment of infection (suspected or confirmed) at the primary site. • Any unexplained use of anti-infective agents in the 30-day period following the primary operation. • Missing post-baseline assessment • Any drainage procedure at the operative site or in and around the peritoneal cavity for infection. • Need for more than one surgical procedure. However, if an independent reviewer considers the initial surgical procedure inadequate, and a subsequent operation is required to correct or reverse the first surgical procedure, then the subject should be considered nonevaluable.	• Concomitant antibiotic at any time for primary surgical site infection or unexplained use • Missing post-baseline assessment • Significant drainage procedure at the operative site or in and around the pelvic cavity for infection APPEARS THIS WAY ON ORIGINAL
Applicant's reasons for clinical non-evaluability (of special note) APPEARS THIS WAY ON ORIGINAL	• A documented preoperative infection exists that requires antibiotic therapy following surgery (e.g. pre-operative positive urine culture) • Requiring delayed primary closure • Antiseptic peritoneal lavage • Initial surgery inadequate (post hoc)	• Concomitant antibiotics administered to treat a distant site infection • Requiring delayed primary closure • Antiseptic peritoneal lavage*

*According to the applicant (12/9/97 e-mail): In the 154-146 study, three subjects received neomycin bowel prep and two subjects were administered triple-sulfa vaginal cream as a packing. All were subsequently rendered not clinically evaluable (App V Table 21.1) during our double-blind review of the evaluability listings. We allowed povidone-iodine or alcohol scrubs, but not as bowel preps or lavages.

APPEARS THIS WAY ON ORIGINAL

8.1 Study 154-128

Protocol Title: "A randomized, double-blind, multicenter trial assessing the safety and efficacy of a single intravenous dose of ALATROFLOXACIN (CP-116,517) compared with cefotetan for the prophylaxis of infection following elective colo-rectal surgery."

APPEARS THIS WAY ON ORIGINAL

8.1.1 Protocol Overview:

Study objective: To compare the safety and efficacy of CP-116,517 (intravenous prodrug of CP-99,219) with cefotetan in the prophylaxis of primary site infection after elective colo-rectal surgery.

Study dates: April 10, 1995 - March 12, 1996