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.

(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.

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.

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).

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

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[c]			
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

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

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.

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.

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 Median Maximum	6.4	7.0
Type of Infection Abscess only Peritonitis only ***Abscess and Peritonitis***	 69 (44%) 60 (38%) 27 (17%)	 67 (44%) 70 (46%) 15 (10%)
Site of Infection ***Multiple***	 19 (12%)	 18 (12%)
Underlying Disease Appendiceal rupture Peptic ulcer perforation ***Post/op abscess or perforation***	 81 (51%) 32 (21%) 32 (21%)	 71 (47%) 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%)

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%)

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Reasons for premature discontinuation were comparable between study arms.

Clinical Efficacy

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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.

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.

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.

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.

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.

APPEARS THIS WAY ON ORIGINAL

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:

> **COMPLICATED INTRA-ABDOMINAL INFECTIONS, including post-surgical infections** caused by *Escherichia coli, Bacteroides fragilis, Streptococcus viridans, Bacteroides thetaiotaomicron, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus faecalis, Streptococcus agalactiae, Streptococcus anginosus, Staphylococcus aureus, Beta Streptococcus* Group B, *Peptostreptococcus* species, *Prevotella* species, *Enterobacter* species, *Enterococcus* species, *Corynebacterium* species, *Fusobacterium* species, *Streptococcus* species or *Bacteroides* species.

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.

APPEARS THIS WAY ON ORIGINAL

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 not 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.

10. Recommendations:

The MO recommends addition of the following information in the INDICATIONS AND USAGE section as it pertains to this indication:

/S/

APPEARS THIS WAY
ON ORIGINAL

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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ON ORIGINAL

TROVAFLOXACIN ADVERSE EVENTS/HEPATOXICITY/PANCREATITIS

Medical Officer's Review
Post-Marketing Adverse Events
NDA 20-759 and 20-760

Dates of Submissions: April 1998 – June 1998
Date MOR Started: May 7, 1998
Date MOR completed: August 31, 1998

Applicant: Pfizer Inc.
235 East 42nd St.
New York, NY 10017-5755

Drug: Trovafloxacin
Alatrofloxacin

Dosage Form: Tablets and IV

APPEARS THIS WAY ON ORIGINAL

Pharmacologic Category: Synthetic Fluoroquinolone

Date of NDA Approval: December 18, 1997

Abbreviations Used:

MO = the current MO, Dr. Alivisatos.
RMO = the pre-NDA medical officer.

Overview:

Trovafloxacin, a synthetic fluoroquinolone for oral administration and alatrofloxacin, the IV formulation, were approved on December 18, 1997 (NDA 20-759, NDA 20-760). The applicant submitted 19 indications for approval with a database of approximately 10,000 patients. A major part of the NDA review was the safety assessment. The majority of the issues which were discovered during the pre-approval NDA review phase related to the CNS and specifically to the development of severe dizziness in all segments of the population but most frequently in young females. Specific attention however was also paid to the assessment of liver abnormalities.

The trovafloxacin NDA review team found no patients in the safety database (0/6500) that developed liver failure or necrosis. Additionally, minor LFT abnormalities were seen in only of the patients studied per indication. The exception to the above was the prostatitis indication. This indication was the sole indication for which information was submitted for a duration of therapy for > 14 days. From a safety standpoint, the MO found, as did the sponsor that, 5/140 trovafloxacin-treated subjects were discontinued due to increased LFTs that were considered treatment-related by the investigator. An additional 10/140 patients developed LFT abnormalities during the course of therapy or immediately after therapy that were not considered treatment-related by the investigators. In the MOR, the MO disagreed with this determination because "the pattern of the abnormalities was consistent with that of the previously listed 5 patients in whom they were attributable to the study drug, both in terms of the timing of the events as well as the duration (approximately 3 – 4 weeks of trovafloxacin usually without an associated increase in bilirubin and with apparent resolution after 6 –10 weeks off therapy. " The MO determined that 14/140 (10%) of treated prostatitis patients developed increased transaminases to ≥ 3x normal after approximately 3 to 4 weeks of therapy. Additionally, 15/140 (10.7%) of prostatitis patients developed an increase of transaminases to ≥ 2 x normal. These abnormalities were not associated with clinical symptoms or with concomitant increases in alkaline phosphatase, bilirubin, or gGT. The LFT abnormalities resolved after therapy with trovafloxacin was discontinued over the course of 6 – 10 weeks. This was compared to an incidence of LFT abnormalities on the comparator ofloxacin arm of 1/132 (0.8%).

At the conclusion of the prostatitis review in July 1997 the MO contacted the applicant and requested that revisions to the proposed labeling with regard to hepatotoxicity be made. The applicant's original proposal was determined to be inadequate and after negotiation during the NDA approval meetings, final labeling was agreed upon by the applicant and the DSPIDPs with regard to this issue. Specifically the original approved label, (pertinent sections at conclusion of document) was determined to accurately reflect the magnitude of LFT abnormalities that were noted during the NDA review. The MO was of the opinion that trovafloxacin induced a chemical hepatitis (i.e. asymptomatic) after > 14 days of therapy and that these abnormalities resolved after 8 – 12 weeks off therapy.

During the review of a periodic report submitted in April, 1998, the MO noted 3 reports of increased transaminases associated with liver biopsy findings of eosinophilic infiltration of the liver in patients who had received trovafloxacin for therapy of less than 14 days duration. At this point on April 30, 1998, the MO contacted HFD-735 to request information about reports of increased transaminases and/or eosinophilic infiltration of the liver associated with trovafloxacin usage.

Concerns with regard to the potential hepatotoxic effect of trovafloxacin had been raised during the IND phase of this antimicrobials development. The MO has provided a brief review of these events below.

Historical Perspective:

The initial trovafloxacin IND The original reviewing MO expressed concern over increased LFTs found in 2/8 dogs studied (increased serum LFTs at 2 months and histologic findings at 6 months). The MO re-reviewed this study (93-783-16, Supplemental Preclinical Information), originally submitted on October 11, 1994 and found that of 8 beagle dogs that received 50mg/kg of the study drug daily for 6 months, 2, a male and a female developed elevations of ALT, AST and gGT during the study. These abnormalities were from 2 to 16 times normal levels. On microscopic exam these enzyme abnormalities were correlated with findings of centrilobular hepatocelluar vacuolar degeneration and necrosis of moderate degree in the male dog and marked in the female. A second group of dogs that received a lower dose of 15 mg/kg daily did not have similar abnormalities and thus a no observed adverse effect level (NOAEL) was established. The MO converted the mg/kg/day dosing schema to mg/m'^2 (utilizing the conversion table of Freireich E. J. et al. Cancer and Chemotherapeutics 50(4): 219 –244, 1966), and found that the 50 mg/kg/day dog dose was equal to a dose of 1000 mg/m'^2. The 15 mg/kg/day dog dose was equal to 300 mg/m'^2. A human dose of 300 mg/day in a 60 kg person or 5 mg/kg/day was equal to 185 mg/m'^2. Therefore there was appeared to be a margin of safety of 5.4 between the toxic animal dose of 50 mg/kg/day and the maximum planned human dose of 300 mg/day. The margin between the NOAEL dog dose of 15 mg/kg/day and the maximum human dose was only 1.6. The MO also compared dog and human Cmax and AUCs at the respective doses and found that at the 50 mg/kg/day dose the dogs had a mean Cmax of 6.7 mcg/mL and an AUC of 40.2 mcg-hr/mL. The human values at the 300 mg dose or 5 mg/kg/day were 4.3 and respectively. The AUCs were comparable because of the longer half-life in humans (10.5 hours) versus dogs (2.5 hours). Thus the animal dose at which toxic effect was found, was extremely close to the maximum planned human dose. This data raised concerns of potential hepatotoxic effects in humans.

Of interest was the finding of hepatic abnormalities in a 6 month rat study
where 3 doses were utilized, a low (25 mg/kg/day), medium (75 mg/kg/day), and high (200 mg/kg/day) dose. As per the pharm/tox reviewer, a higher incidence of minimal to mild hepatic fatty change was noted in the mid- (7/15) and high (11/15) dose males relative to the low dose (4/15) and the control (4/15) males.

The original RMO reviewing the planned Phase II protocols requested that clinical studies be limited to 14 days duration and at the end-of-Phase II meeting, August 29, 1994, it was requested that prior to proceeding to Phase III studies, the applicant perform a study to assess the reversibility of these hepatic lesions in dogs. This study (94-783-23) was performed at a dose of 50 mg/kg/day for 6 months. 4/16 dogs were found to have increased LFTs (primarily ALT), which returned to baseline after treatment discontinuation on days 67 to 89. There was microscopic correlation, that is findings of hepatocelluar

necrosis and periportal infiltration in 3 of the animals. The histologic changes were all found to be reversible at necropsy.

At this point the original RMO determined that it was safe to proceed with all planned Phase III studies of < 14 days duration of therapy as well as the prostatitis study. This study was originally planned for 6 weeks duration, however it was allowed to proceed only after the duration of therapy was limited to 4 weeks for the trovafloxacin-treated patients. Additionally, the RMO revised the protocol to provide for laboratory reevaluations at day 21 of the study and weekly thereafter.

Current Trovafloxacin Labeling (as approved 12/97):

WARNINGS: " Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported in patients receiving therapy with all antibiotics. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions, vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial nephritis, acute renal failure or insufficiency, **hepatitis, jaundice, acute hepatic necrosis or failure...**

PRECAUTIONS: "Because TROVAN® can cause elevations of liver function tests during or soon after prolonged therapy (i.e. ≥ 21 days), periodic assessment of hepatic function is advisable. The safety and efficacy of TROVAN® given for > 4 weeks have not been studied."

ADVERSE REACTIONS: GASTRONINTESTINAL: "abdominal pain, altered bowel habit, constipation, diarrhea-Clostridium difficile, dyspepsia, flatulence, loose stools, gastritis, dysphagia, increased appetite, gastroenteritis, rectal disorder, colitis, pseudomembranous colitis, enteritis, eructation, gastrointestinal disorder, melena, hiccup."

LABORATORY CHANGES: Changes in laboratory parameters without regard to drug relationship, occurring in > 1% of TROVAN®-treated patients were: " increased ALT (SGPT), increased AST (SGOT), and alkaline phosphates;...It is not known whether these abnormalities were caused by the drug or the underlying condition being treated."

"The incidence and magnitude of liver function abnormalities with TROVAN® were the same as comparator agents except in the only study in which oral TROVAN® was administered for 28 days. In this study (chronic bacterial prostatitis), 9% (13/140) of TROVAN®-treated patients experienced elevations of serum transaminases (AST and/or ALT) of ≥ 3 times the upper limit of normal. These liver function test abnormalities generally developed at the end, or following completion of, the planned 28-day course of therapy, but were not associated with concurrent elevations of related laboratory measures of hepatic function (such as serum bilirubin, alkaline phosphatase, or lactic dehydrogenase). Patients were asymptomatic with these abnormalities, which generally returned to normal within 1 – 2 months after discontinuation of therapy."

APPEARS THIS WAY ON ORIGINAL

Post-marketing Events:

Subsequent to the review of a periodic report submitted in April, 1998, wherein MO noted 3 reports of increased transaminases associated with liver biopsy findings of eosinophilic infiltration of the liver in patients who had received trovafloxacin for therapy of less than 14 days duration and after reviewing the animal and human trovafloxacin-related hepatotoxicity data from the IND and NDA phases of development (see above), the MO presents post-marketing case reports submitted both to Pfizer and to the agency through June 30, 1998. The Pfizer-generated reports were submitted to the DSPIDPs after the institution of a Trovan®-monitoring system to capture all hepatic and pancreatic AEs meeting a case definition proposed by the review team. This case definition was communicated to Pfizer over the course of 2 telecons on May 12 and 14, 1998, and after the receipt of additional reports of hepatotoxicity as well as pancreatitis.

During the aforementioned telecons, Pfizer agreed to submit all serious as well as non-serious reports meeting the case definition to the DSPIDPs within 15 days of receipt. They agreed to communicate with the reporters and to ask event-specific follow-up questions as requested by the MO. This agreement included the review of all in-house non-serious reports already received by Pfizer and held for the next planned periodic report. Terms that contributed to a hepatitis case-definition included the finding of one of the following verbatim terms in the text of a MedWatch form:

- Hepatitis
- Hepatic Enlargement or Hepatomegaly (as evidenced by physical exam or abdominal US or CT or MRI)
- Pancreatitis
- Liver biopsy
- Liver transplantation
- Jaundice
- Right upper quadrant pain
- Elevated LFTs (AST, ALT, and Alk. Phos, or bilirubin)

The elevation of LFTs as evidenced by the finding of:

- AST or ALT > 2 x ULN (where normal ranges reported), or > 80 if normal ranges not known
- Alkaline phosphatase > 2 x ULN
- Direct bilirubin > 1.0 mg/dL or indirect bilirubin > 3.0 mg/dL
- Amylase > 2 x UNL

Specific follow-up questions were outlined as follows:

- History of previous fluroquinolone usage in the recent or distant past.
- History of other liver disease risk factors including ETOH, DM, medications, viral etiologies, GB or BT disease.
- Complete enzyme and bilirubin profile
- Time to resolution of the condition
- CBC with differential to assess for eosinophilia
- Liver biopsy results.

At the time this document was prepared, the agency was in receipt of 38 case reports, 11 serious and 27 non-serious. 7 cases were of pancreatitis, 31 of hepatitis (with 1 patient with both). No deaths had been reported. All cases are prefaced by the MCN (manufacturer's control number), a seven-digit number. Few cases were reported directly and only to the agency and are prefaced by a 4 to 6-digit number only. In cases where reports were received by both Pfizer and the agency, the MCN was utilized. Concurrent to the preparation of this document an electronic dataset was instituted (Microsoft Access) and is currently in use.

After the review of the cases (see below), the review team determined that a labeling change was necessary as the originally-approved label did not adequately convey the magnitude or the timing of the observed trovafloxacin-related hepatotoxicity. In an effort to determine the type of change needed (i.e. WARNING or not) as well as the mode of communication of the proposed change to practicing physicians (Dear Doctor letter), the MO compared the observed trovafloxacin AEs with the hepatic events associated with other approved quinolone antimicrobials within the first year after approval.

Comparison with Other Quinolone Antimicrobials:

Trovafloxacin: approved 12/97

To date: 179 AEs reported: 9 serious liver and 21 non-serious liver
Total Liver: 30
Total Pancreatitis: 8 (1 with hepatitis serious, 2 serious and 5 NS)

274,000 oral prescriptions to date (IMS Health's NPA Database: prescriptions filled by retail and outpatient pharmacies)

Ciprofloxacin: Approved 10/87
1st yearly report: 375
Total liver: 21

Floxin: Approved 12/90
1st yearly: 388 total
Total liver: 9

Levofloxacin: approved 12/96:
1st yearly: 426
Total liver: 10
470,000 oral prescriptions

Sparfloxacin 12/96: to date 81total reports, 1 liver
8000 oral prescriptions

Grepafloxacin 11/97: 13 total, no liver
105,000 oral prescriptions

Temafloxacin: 1/92
1st year: 1621
Total liver (including hemolytic anemia) 212

All AEs/liver/2nd Quarter after approval and 1st Year cumulative

Drug	2nd Quarter ALL	2nd Quarter liver	1st Year ALL	1st year liver	# oral prescriptions
Trovafloxacin (12/97)	181	34	-	-	274,000 (to date)
Ciprofloxacin 10/87	114	9	375	21	Not available
Ofloxacin 12/90	91	5	388	9	Not available
Levofloxacin 12/96	182	3	426	10	470,000 (first 6 months)
Sparfloxacin 12/96	32	0	81	1	8000 (first 6 months)
Grepafloxacin 11/97	23	0	-	-	105,000 (first 6 months)
Temofloxacin 1/92	255	47 (26)*	1621	212 (76)*	Not available

* # in parentheses represents cases of hemolytic anemia.

Comment: From the above table and text it became apparent that trovafloxacin had the most reported liver-associated AEs within the first 6 months after approval of any of the approved and on the market quinolone antimicrobial agents. Only temofloxacin (withdrawn in 6/92) had a larger number of reported events. The comparative incidence of hepatic events reported in the first year after approval could not be

events. The comparative incidence of hepatic events reported in the first year after approval could not be assessed for trovafloxacin. With regard to the denominator, that is the number of prescriptions filled at the time this data was collected, the information provided by is limited in that it refers only to the oral formulation and not to the IV. However, the limited data from levofloxacin, grepafloxacin and sparfloxacin (34 reports of trovafloxacin-related liver toxicity in the face of a denominator of at 274,000 as compared to levofloxacin with only 3 reports of liver toxicity despite its higher usage as expressed by a denominator of 405,000) serve to illustrate the magnitude of the trovafloxacin-related hepatotoxicity as compared to other approved quinolones.

Temofloxacin experience

During the IND and pre-NDA phases of trovafloxacin drug development concerns were raised by the preclinical and clinical reviewers over the similarities in chemical structure between the temofloxacin and trovafloxacin molecules (see attached). The only difference in chemical structure was the substitution of an aza-bicyclo-hexyl ring at the 7th position of the trovafloxacin molecule as compared to the temofloxacin molecule where a piperazine ring could be found at the 7th position.

This similarity was of concern because shortly after the temofloxacin approval in January 1992 and during the 2nd quarter of 1992, an increased incidence of AERs were noted with hemolytic uremic syndrome. The evaluation and description of these cases led to the negotiated withdrawal of temofloxacin.

Patients typically presented with fever, chills, and jaundice between 5 –7 days after starting therapy with temofloxacin. Renal failure, DIC and hemolysis were noted with accompanying decreases in hemoglobin, hematocrit and platelet counts. Renal dysfunction necessitating dialysis was found in 63% of the cases described. Concomitant LFT abnormalities were noted usually expressed as an increase in AST and total bilirubin. An immunologic mechanism was postulated because of a strong association found between prior use of a quinolone and development of the syndrome.

Despite the structural similarity between trovafloxacin and temofloxacin, there were notable differences in the presentation of patients with the presumed trovafloxacin-generated hepatitis as compared to the more complex multisystem illness seen in patients who had received temofloxacin including deaths attributed to temofloxacin-associated hemolytic anemia/rhabdomyolyis as well as the increased number of hospitalizations and dialysis required by the patients.

Described below are the 11 serious reports followed by the 27 non-serious. Presentation is in order of receipt.

Serious Case Reports (N = 11):

- 9805098 and 9809955: Reported 2/28/98: 44 YO F on trovafloxacin for pneumonia for 10 days. Discontinued for 2 days and then took another 2 days (received a total of 12 days). Finished R/x by 2/4 or 2/10. The patient then developed RUQ pain and elevated LFTs. A CT revealed liver enlargement and a very edematous gallbladder and LFTs continued to increase. A GI consultant saw the patient on 2/14/98 and performed an emergency cholecystectomy on 2/17. A liver biopsy revealed changes possibly consistent with recent antibiotic use *(eosinophilic infiltration and Kuppfer cell hyperplasia)*. As per the reporter, this patient did not have an elevated alkaline phosphatase or bilirubin. The ALT reached the 600 range and there was a previous history of prior (lifetime) quinolone usage (levofloxacin for chronic sinusitis). This patient had no history of liver disease, ETOH usage or use of other medications.

MO Comment: *This case was the most typical. The patient, a healthy female developed evidence of an eosinophilic hepatitis with no other obvious etiology. Notable is the different histopathology from that seen in the preclinical dog studies.*

- 9809892: reported 4/16/98: A female patient received trovafloxacin for 2 weeks for chronic sinusitis. She was hospitalized (3 weeks post-R/x) on 4/6 for a viral syndrome with fever, elevated LFTs and was diagnosed with pancreatitis. CT revealed pancreatic enlargement accompanied by mesenteric infiltration. Amylase and lipase remained within normal limits. Transaminases . Also had a transient rash. Trovafloxacin was discontinued on 4/6 and she improved. No further information was provided other than that there was no history of ETOH usage.

MO Comment: *This is the only case of pancreatitis with concomitant hepatitis. As opposed to the other pancreatitis cases, this patient developed disease 3 weeks after the conclusion of therapy.*

- 9808576: 74 YO F with LLL pn/nia received trovafloxacin for 10 days (2/13 – 2/23/98). Presented 3 weeks later (3/11/98) with elevated LFTs and fever and was admitted to the hospital. Specifically had temp watery diarrhea and an AST ALT The reporting MD stated that her alkaline phosphatase and bilirubin were within normal limits. CBC revealed an *eosinophilia* (not available). A work-up for viral hepatitis was negative (A, B and C). The patient improved spontaneously with regards to fever and diarrhea and has had a progressive decrease in her LFTs A repeat test is pending. This patient had no history of liver disease, ETOH usage or use of other medications. *Clostridium difficile* workup was negative.

MO Comment: *The etiology of the patient's clinical picture is uncertain. The presence of fever and diarrhea suggest an infectious etiology, however, the presence of eosinophilia is of concern.*

- 9810538: 38 YO diabetic F with a diabetic foot ulcer and sepsis received trovafloxacin 300 mg IV qd from 4/10 – 4/12/98. Patient also received Diflucan® for an unspecified period and dose. Other R/X included Timentin®, Synthroid®, IN, Pepcid®, Lasix, Elavil, Zosyn®, Vancomycin, and Darvocet. There were no LFTs performed prior to 4/12/98. On that date the patients became jaundiced and lethargic and a chemistry profile revealed normal transaminases (ALT AST , a bilirubin and an alkaline phosphatase The patient was moved to the ICU where she recovered over the next few days. Final values were bilirubin) and Alk. Phos: Final LFTs not provided. The past medical history was notable for IDDM, CHF, CRF, CVA, hypothyroidism, and diabetic neuropathy. There was no history of Tylenol (other than Darvocet) or ETOH usage.

MO Comment: *Clinical picture inconsistent with rest of cases. Multiple medical problems lead to difficulty in attribution to trovafloxacin.*

- 98010252: 50 YO Female with a history of pneumonia with hospitalization for pancreatitis after 1 - 2 days of trovafloxacin. Positive history for diabetes. Trovafloxacin 200 mg PO qd was started on the day of hospitalization.

MO Comment: *The MO determined that this case was unlikely to be related to trovafloxacin as the patient developed pancreatitis on the first day of therapy.*

- 9810885: 56 YO male with hospitalization for pancreatitis after 2 days of trovafloxacin at a dose of 300 mg PO qd started on 4/13. Also had unspecified history of cancer.

- 7927: purpura: 32 YO DM F received 7 days of trovafloxacin 200 mg PO qd from 2/26. The patient developed increased Alk. Phos , ALT and AST as well as a "purple nose" Patient has a history of vasculitis. .

MO Comment: *Underlying vasculitis could cause this clinical picture.*

- 9811689: 29 YO F on a Swiss trovafloxacin pneumonia study on 12/31/97. Received 200 mg PO qd through Jan 18, 1998. (19 days r/x). The patient developed empyema and required transfer to ICU on January 4, 1998 where she was found to have elevated LFTs. Report mentions nonspecific history of

liver disease. Concomitant medications included paracetamol, tramadol, nadroparin, salbutamol, and ipratropiumbromid. LFTs on 12/31: LDH: , AST ALT Alk Phos Labs from 2/98 were wnl.

- 9809169 (83447) 49 YO male received trovafloxacin from 3/9 through 3/18. (NOTE only 7 doses taken). Patients had a history of sinusitis and allergic rhinitis. The patient also received ceftriaxone from 3/22 – 3/25. On 3/19 and prior to alternative antimicrobials, the patient developed cholecystitis which led to a cholecystectomy and hepatitis. Pleural and pericardial effusions as well as bullous skin lesions and a peripheral *eosinophilia* were also present, thus suggesting an allergic process. LFTs: A Phos: AST: ALT Bili: Hep A and C Patient had a HepBSAb (vaccine).

- 83816: 38 YO male received 200 mg trovafloxacin PO qd for 10 days. Also received Entex and Tylenol for sinusitis. After 2 – 3 days patient improved clinically and finished his course. 3 days post-therapy, patient presented complaining of fatigue. On 5/4 had a temp to 101. Saw original MD again, 10 days after stopping trovafloxacin. At that time he had dark urine, and RUQ tenderness. Physical exam revealed abdominal distention consistent with the presence of ascites. Lab: AST ALT: T Bili: Bili: CMV IgG elevated, hepatitis workup negative, peripheral eosinophilia present CT: ascites and increased liver size. There was no significant PMH and the patient drank approximately 3 beers a week. No baseline LFTs available. Latest LFTs: AST ALT Alk. Phos Bili

- 9815470: 38 YO male ER nurse received trovafloxacin for 10 days for recurrent sinusitis. Previously received clarithromycin without relief. Approximately 6 days post-therapy the patient had an elevated temperature associated with an achy feeling. He also stated that he felt disoriented. The patient continued to have increasing weakness and 2 – 3 days later developed nausea and vomiting. 1 day later he had to leave work because of high fever, burning and nausea. In the ER the patient was found to have a tender liver and elevated LFTs and increased bilirubin INR A CT scan was performed, no GB disease was found and he was discharged with a preliminary diagnosis of hepatitis. The next day he was unable to care for himself and was admitted for confusion. A liver biopsy was performed and then the patient was transferred to a tertiary care center where acute liver failure was diagnosed. The patient had evidence of edema and ascites. Biopsies from both institutions were similar and revealed zone 3 liver necrosis, no cirrhosis, eosinophilic infiltration, evidence of veno-occulusive disease and disseminated venulitis. The patient had evidence of portal hypertension with occlusion of the middle hepatic artery as well as hepatofugal flow (elevated R arterial pressure. versus normal Right lobe of liver
  Assuming the need for transplantation he received steroids and diuretics and improved to the point of discharge. Transient renal dysfunction developed due to dye studies. Transplantation on hold at present. Previous history of quinolone use not known. LFTs improved. The patient had a remote history of exposure to paint stripper and a tractor accident. Additionally, he had been receiving Motrin. Follow-up obtained from MD (Chief GI), patients, and pharmacist. Further information is pending.

MO Comment: *This case is the most severe of those reported to date. At this point further information is not available with regards to previous quinolone usage. This case and the first case are similar in that eosinophilic infiltration was seen in the biopsy material from both patients. Based on the available information, an immunologic mechanism (hypersensitivty reaction) can be postulated.*

MO Comment*: Of the 11 serious reports listed above, 8 were reported to the agency and to Pfizer and 3 only to the agency. 3/11 (27.2%) had evidence of pancreatitis and 8/11 (72.8%) of the patients had evidence of hepatitis. Outcome appears to have been resolution in most cases where information has been provided.*

Non-serious Case Reports (N = 27)

- 9804918: Hospitalized patient received trovafloxacin 200 mg IV qd for surgical prophylaxis for a cholecystectomy. After 2 days patient was found to have an elevated bilirubin and therapy was discontinued.

- 9805225: 60 YO female received trovafloxacin 300 mg IV qd for pneumonia. Approximately 7 days after the start of therapy, the patient had a total bilirubin reported as doubled as well as an Alk. Phos. , AST) and gGT . Patient was also receiving TPN.

- 9805226: Unknown demographics and dosage. Reported that a patient developed pancreatitis after 2 days of trovafloxacin.

- 9805396: Unknown demographics and dosage. Reported that a patient developed pancreatitis after 2 days of trovafloxacin.

- 9805497: 51 YO female received trovafloxacin 200 mg PO qd. After 4 days of therapy, the patient developed a rash. In addition and at an unknown timepoint, the patient was noted to have abnormal LFTs. An ultrasound was negative for gallstones and the reporter suspected hepatitis secondary to trovafloxacin.

- 9806570: 69 YO male received trovafloxacin 200 mg PO qd for gangrene (3/4/98). 4 days after the start of therapy (3/8/98), the patient developed an increase in creatinine which peaked day 7 (3/10/98). On 3/9/98 the patient received an IV dose of alatrofloxacin. 6 days after the start of therapy the patient was also found to have increased LFTs with ALT and AST LDH was Bili Relevant PMH included liver disease, ETOH abuse, and diabetes.

- 9807737: Hospitalized female received alatrofloxacin 300 mg IV qd for an unknown indication. After 2 –3 doses, she developed elevated LFTs with subsequent improvement after discontinuation.

- 9808005 (also reported as 9807717): 63 YO male received alatrofloxacin 200 mg daily for pneumonia. After 4 days of therapy, the patient developed elevated LFTs and therapy was discontinued on day 10. The patient subsequently improved.

- 9808037 (also reported as 9807718): An elderly female received intravenous alatrofloxacin (200 mg) followed by oral trovafloxacin at a dose of 200 mg qd for unspecified periods. Underlying diagnosis was bilateral pneumonia. The patient developed a gGT to three times normal. There was a PMH of diabetes controlled by diet and no further follow-up.

- 9808955: 80 YO male received trovafloxacin 200 mg PO qd for a RT infection as of 3/28. On 3/30 he was found to have an elevated creatinine and BUN. On 3/31 the reporter also stated that the patient had an elevated LDH and SGOT. These were attributed to the patient's underlying disease, multiple myeloma. No further info was provided.

- 9809169 (83447): Unknown demographics: patient developed eosinophilia, elevated LFTs and cholangitis while on trovafloxacin.

- 9811665: Unknown patient developed elevated LFTs after 10 days of trovafloxacin therapy.

- 9811667: Unknown patient developed elevated LFTs after 10 days of trovafloxacin therapy.

- 9811958: 54 YO male received trovafloxacin 200 mg PO qd for prostatitis for 28 days. On day 30 he was found to have elevated LFTs: ALT), AST Bili , A Phos and LDH.

- 9812385: 92 YO female with diverticulitis and no underlying liver disease received trovafloxacin 200 mg a day. She also received Tylenol. Patient developed jaundice and an ultrasound and hepatitis workup were negative. The GI consultant attributed the jaundice to therapy.

- 9813438: Unknown patient with unspecified LFT elevation.
- 9814273: Male received trovafloxacin 200 mg PO qd for prostatitis. Developed jaundice and weakness with hepatitis attributed to trovafloxacin.
- 9814453:A patient with sinusitis received trovafloxacin 200 mg qd and developed hepatitis.
- 9811020: 64 YO female started 200 mg trovafloxacin qd on 4/3. On 4/14, day 12 developed generalized muscle aches and joint pains associated with dry mouth and headache. Trovafloxacin discontinued on 4/16 (day 14). LFT increase noted on 5/5.
- 9815753: female received trovafloxacin for 20 days for sinusitis. LFT increase noted post-therapy. Patient was symptomatic with weakness and malaise.
- 9815755: Male patient received trovafloxacin for 28 days for prostatitis. After completion had an SGOT
- 9815758: 66 YO male received alatrofloxacin IV. After 3 days was noted to have elevated BUN and creatinine as well as increased LFTs (bilirubin, LDH and SGOT . Dose decreased.
- 9815975: 62 YO male IDDM developed pancreatitis 9 days after starting alatrofloxacin 300 mg IV QD after a CABG. The patient developed fever accompanied by an amylase , and a lipase There was gradual resolution of the pancreatitis over the next 3 weeks with a final amylase . The patient was receiving multiple concomitant medications including furosemide, famotidine, midazolam, dopamine and fentanyl.
- 9815973: 59 YO male developed pancreatitis 9 days after starting IV alatrofloxacin 300 QD as empiric Gram (+) coverage after small bowel resection. Concurrent medications included vancomycin, furosemide, famotidine, digoxin, diltiazem and clonidine. The initial amylase , and lipase was The enzyme elevations were accompanied by fever and gradually resolved over a week.
- 9816101: unknown patient developed elevated LFTs after IV alatrofloxacin.
- 9817642: unknown patient developed elevated LFTs in less than a week on trovafloxacin.
- 9818538: (84288): Tremors and confusion developed in a patient after 7 days of IV alatrofloxacin 300 mg qd. The patient also received 1 PO 200 mg dose. LFTs were elevated with an AST and an Alk Phos No eosinophilia was noted and the patient had a history of no quinolone usage in the last 4 years.

Comment: Of the 27 additional cases provided 4 were of pancreatitis bringing the total to 7. 2 of the additional pancreatitis cases were similar to the 2 of the 3 serious pancreatitis cases in that the pathology appeared to develop within 2 days of the start of therapy. In the remaining 2 cases, pancreatic disease with amylase and lipase elevations accompanied by fever developed 9 – 10 days into a course of alatrofloxacin therapy.

Based on the above, the MO performed cumulative statistics (see below) in an attempt to describe the epidemiology of the trovafloxacin-related hepatic and pancreatic events. Unfortunately and a common pitfall of this method of AE reporting was the scanty information provided as well as the difficulties encountered in contacting the individual reporters.

Cumulative Statistics:

Pancreatitis (N = 7):