CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020759/020760

MICROBIOLOGY REVIEW(S)

NDA
520

Division of Anti-Infective Drug Products
Clinical Microbiological Review

DEC 29 1997

NDA NUMBER:	REVIEW DATE:	SUBMISSION/TYPE:
20-759 20-760	10-31-97	Original NDA
DOCUMENT DATE	**CDER DATE**	**ASSIGNED DATE**
12-27-96	12-30-96	1-21-97

NAME & ADDRESS OF APPLICANT:

Pfizer Central Research
Medical Research Laboratory
Eastern Point Road
Groton, CT 06340

CONTACT PERSON:

Ronald I. Trust, Ph.D., Associate Director
Pfizer Central Research
Medical Research Laboratory
Eastern Point Road
Groton, CT 06340
Phone Number: (860) 441-6991

DRUG PRODUCT NAME

Proprietary: Trovan
Trovan I.V.

Nonproprietary/USAN: Trovafloxacin Mesylate tablets
Alatrofloxacin Mesylate I.V.

Code Names/#'s: CP-116,517-27; CP 99,219;

Therapeutic Class: 1 S

PHARMACOLOGICAL CATEGORY: Fluoroquinolone

DOSAGE FORM: Tablets
Aqueous concentrate injection

STRENGTHS: 100 and 200 mg/tablet
5 µg/mL, solution

ROUTE OF ADMINISTRATION: Oral
Intravenous infusion

DISPENSED: _X_ Rx ___ OTC

RELATED DOCUMENTS (if applicable):

INDs.

REMARKS/COMMENTS:

This application is for a fluoroquinolone, trovafloxacin. The application is for the treatment of patients with nosocomial pneumonia; community acquired pneumonia; acute bacterial exacerbation of chronic bronchitis; acute sinusitis; complicated intra-abdominal infections, including post-surgical infections; gynecologic and pelvic infections, including post-surgical infections; surgical prophylaxis; skin and skin structure infections; uncomplicated urinary tract infections; uncomplicated urethral, cervical pharyngeal and rectal gonorrhea; nongonococcal urethritis and cervicitis; pelvic inflammatory disease.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY section of the package insert. The changes needed should be sent to the sponsor. These revisions are listed as notification to the sponsor at the end of this review on pages 126-137.

TABLE OF CONTENTS

I. INTRODUCTION

Trovafloxacin is a new fluoronaphthyridone antimicrobial structurally related to the fluoroquinolones, and containing a novel 6-amino-3-azabicyclo-hexane side chain at position 7. Trovafloxacin compared with ciprofloxacin is somewhat more active against Gram-positive organisms. Against *Streptococcus pneumoniae* the median MIC_{90} of trovafloxacin for 1,867 strains is 0.125 µg/mL. It is equally active against penicillin-susceptible and -resistant pneumococci. Trovafloxacin is somewhat more active than ciprofloxacin, ofloxacin, and sparfloxacin against staphylococci. Like other fluoroquinolones trovafloxacin is also active against fastidious organisms that are associated with respiratory tract infections including *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*. It is as active as ciprofloxacin against ciprofloxacin-susceptible *Neisseria* spp. Trovafloxacin is also active against ciprofloxacin -resistant gonococci. Trovafloxacin is less active than ciprofloxacin against the *Enterobacteriaceae*, being fourfold less active against many species and as active against others. Trovafloxacin is about twofold less potent than ciprofloxacin against *Pseudomonas aeruginosa*. Trovafloxacin is bactericidal against facultative and aerobic organisms, with minimum bactericidal values being fourfold above the MIC. Trovafloxacin's *in vitro* activity against anaerobes such as *Bacteroides* and *Prevotella* spp. and distinguishes it from other fluoroquinolones. The MIC_{90} of trovafloxacin for 1,404 *B. fragilis* strains ranged

Trovafloxacin is rapidly absorbed after oral dosing, possesses extensive tissue distribution and an elimination half-life of 10-12 h, allowing once-daily dosing. Trovafloxacin is 70-88% bound to plasma proteins and is concentrated up to 28-fold in PMNs and macrophages. Elimination appears to be primarily by the biliary route. Trovafloxacin appears to have low potential for phototoxicity and it does not antagonize the metabolism of theophylline. A highly soluble L-ala-L-ala prodrug, alatrofloxacin, has been designed for intravenous administration. *In vivo*, alatrofloxacin is rapidly and completely hydrolyzed to trovafloxacin. Intact alatrofloxacin has poor antimicrobial activity, with MICs of ≥50 µg/mL against many clinical isolates of bacteria.

The clinical indications for trovafloxacin/alatrofloxacin are: sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, nosocomial pneumonia, complicated and uncomplicated skin and skin structure infections, uncomplicated (b)(4) urinary tract infections, prostatitis, gonorrhea, pelvic inflammatory disease, nongonococcal urethritis and cervicitis, acute pelvic infections, complicated intraabdominal infections, epidemic meningococcal meningitis and surgical prophylaxis.

II. PRECLINICAL EFFICACY (IN VITRO)

A. Mechanism of Action

1. Primary Mechanism of Action

Biochemical and genetic evidence indicates that both DNA gyrase (a type II topoisomerase) and topoisomerase IV are antibacterial targets for trovafloxacin. Topoisomerases are enzymes found in all cells which alter the topological state of DNA. To date, four topoisomerases have been identified in *E. coli* and other species of bacteria(1,2). Studies using purified enzymes have indicated that fluoroquinolones are not potent inhibitors of two of these enzymes, topoisomerases I and III. The type II topoisomerase, DNA gyrase, is the sole enzyme in the bacterial cell capable of introducing negative supercoils into DNA. This enzyme, in concert with topoisomerase I, functions to maintain the appropriate superhelicity of DNA in the cell, which is critical for many cellular processes such as replication and transcription. Extensive studies with drug-resistant mutants and cell-free gyrases have provided evidence that fluoroquinolones elicit their bactericidal action by interacting with DNA gyrase(3). Work from several laboratories has described a second type II enzyme in bacterial cells, topoisomerase IV that appears to play a key role in the partitioning of chromosomal DNA during cell division (6,7).

E. coli DNA gyrase consists of two subunits A and B with molecular weights of 97 and 90 kDa, respectively (3). Functional DNA gyrase consists of an A_2B_2 complex. Mechanistically, gyrase makes a double strand break in one strand of DNA, leading to an intermediate characterized by covalent bonds between the 5′ phosphates of the broken DNA strands and the tyrosine 122 hydroxyl groups of each gyrase A subunit. This "cleavable complex" allows a second double strand of DNA to pass through the broken sequence. Following strand passage, gyrase reseals the double strand cut, completing the strand-passage reaction (4). The A subunits of gyrase, as mentioned above, are responsible for catalyzing the double strand breakage and reunion of DNA, the energy for which is supplied by hydrolysis of ATP. The B subunits carry out the ATP hydrolysis reaction.

The role of fluoroquinolones as inhibitors of the DNA strand passage reaction has been elucidated through experiments employing sodium dodecyl sulfate to disrupt a ternary complex created by gyrase, DNA, and bound quinolone (3). The available data indicate that fluoroquinolones exert their inhibitory effect on gyrase by binding to a complex created by gyrase and DNA. A partially unwound region of DNA undoubtedly exists in this complex, allowing the drug to enter a "binding pocket" consisting of conserved amino acid residues from the A subunit of gyrase, and single stranded DNA (3).

Productive drug binding and "freezing" of the cleavable complex by the fluoroquinolone creates a cellular poison that is responsible for the bactericidal activity of these agents. It has been found that formation of the drug-gyrase-DNA complex prevents passage of polymerases necessary for DNA and cellular replication (5). This mechanism of cell death would also explain why the wild type *gyrA* allele is dominant over mutant *gyrA* in a merodiploid bacterial cell containing copies of both genes. In such a cell, the chromosomally encoded mutant gyrase would be refractory to the action of the quinolone. However, the presence of normal gyrase enzyme (encoded on a plasmid) would restore the drug's capability to form a lethal complex in the cell. This poison hypothesis is important in understanding the lethal action of quinolones against bacteria.

Topoisomerase IV, on the other hand cannot supercoil DNA. This enzyme can relax DNA *in vitro* but its preferred catalytic activity is decatenation, a reaction that is favored over relaxation by a margin of up to 10 to 1 when specific activities are compared *in vitro* (6-8). Studies with

temperature-sensitive mutants of *E. coli* first revealed the important role of topoisomerase IV in cell division (8). DNA gyrase can only partially compensate for topoisomerase IV in such temperature-sensitive cells, indicating that topoisomerase IV is essential for proper cell growth. Topoisomerase IV is thought to be a membrane-bound enzyme, consistent with its key role in chromosome partitioning (6).

Reports from several investigators have indicated that nalidixic acid and the fluoroquinolones are 3- to 30-fold less potent against *E. coli* topoisomerase IV than they are against DNA gyrase, as judged by inhibition of enzyme activity (6,8). This, coupled with initial failure to obtain quinolone-resistant mutants in *E. coli* that mapped to topoisomerase IV, led investigators to conclude that this enzyme was not a primary target for fluoroquinolones. Evidence suggests, however, that this relationship may be different in *S. aureus* and other Gram-positive organisms. Ferrero *et al.* (9) used the polymerase chain reaction (PCR) to amplify the quinolone resistance determining region (QRDR) of gyrA and grlA (the topoisomerase IV homolog) in clinical isolates of *S. aureus* showing varying levels of resistance to fluoroquinolones. Isolates with ciprofloxacin minimum inhibitory concentrations (MICs) between 2 and 16 μg/mL had changes only in *grlA*, which led to substitution of Phe or Tyr for Ser 80 in the GrlA subunit. Strains with MICs >32 μg/mL (and one with an MIC of 16 μg/mL) had changes in both the GrlA and GyrA subunits (9). A second study from this group used step-wise laboratory selection to assess the changes that conferred ciprofloxacin resistance in *S. aureus* (10). In agreement with their first study, these investigators found that first-step mutants (MIC to ciprofloxacin of 2 μg/mL) had a substitution of Ser 80 by Tyr or Glu 84 by Lys in the GrlA subunit. Mutants with higher levels of resistance to ciprofloxacin (MIC 128 μg/mL) all exhibited changes in GyrA in addition to a GrlA mutation. The conclusion derived from these studies was that, at least in *S. aureus*, topoisomerase IV appears to be a primary target for fluoroquinolones (9,10). Enzyme inhibition studies using purified topoisomerase IV from *S. aureus* have not yet been reported. This new information regarding topoisomerase IV may be relevant in explaining the improved potency of some new fluoroquinolones such as trovafloxacin against Gram-positive organisms.

The inhibitory activity of trovafloxacin against purified DNA gyrase of *E. coli* has been studied (11). The lowest amount of trovafloxacin which stimulated gyrase-mediated DNA cleavage *in vitro* was 0.78 μg/mL (1.9 μM), compared with 0.26 and 0.14 μg/mL for ciprofloxacin and sparfloxacin, respectively (11). In the same study, the MIC_{90}s against 40 clinical isolates of *E. coli* were 0.125, 0.062, and 0.062 μg/mL for trovafloxacin, ciprofloxacin, and sparfloxacin, respectively. As observed previously, the amount of fluoroquinolone required to inhibit the activity of purified gyrase *in vitro* is higher than that required to inhibit cell growth. In another report (12) trovafloxacin was ten-fold less potent at inhibiting the relaxation activity of *E. coli* topoisomerase IV (IC_{50} of 8.5 μM) than it was against the supercoiling activity of DNA gyrase (IC_{50} of 0.8 μM). Genetic evidence suggests that topoisomerase IV is a primary target for trovafloxacin in the Gram-positive organism *Streptococcus pneumoniae* (13).

2. Additional Mechanisms of Action

While the principal mechanism of action for fluoroquinolones is thought to involve inhibition of bacterial DNA gyrase and topoisomerase IV, other mechanisms are thought to be involved as well.

Many quinolones have been included in a series of studies aimed at characterizing their bactericidal mechanism of action (14). It has been shown that the quinolones possess four bactericidal mechanisms of action, designated as mechanisms A, B, B_1 and C. Mechanism A, the basic quinolone mechanism, is the sole mechanism of action shown by older quinolones such as nalidixic acid. This mechanism requires bacteria to be undergoing multiplication and protein or RNA synthesis (14). Mechanism B is an additional mechanism possessed by several modern quinolones (15). This bactericidal mechanism is active against non-dividing bacteria and does not require active protein or RNA synthesis. A related bactericidal mechanism, B_1, has also been identified, but only with clinafloxacin; this mechanism does not require protein or RNA synthesis but does require dividing bacteria (16). Mechanism C, on the other hand, does not require bacterial multiplication, but does require active protein or RNA synthesis. This mechanism has been found with norfloxacin and enoxacin (17) only.

It has been suggested that the failure of ciprofloxacin to eradicate some staphylococcal infections may be due to a lack of an additional bactericidal mechanism B, B_1 or C (18). A study examining trovafloxacin for these properties (18) found it to have a typical quinolone biphasic (U-shaped) dose response curve for killing of *E. coli*, *S. aureus*, and *S. pneumoniae*. It was noted that the optimum bactericidal concentration (OBC) for trovafloxacin against *S. pneumoniae* C3LN4 was 1.5 µg/mL compared with 5.0, 5.0, and 15.0 µg/mL for ciprofloxacin, levofloxacin, and ofloxacin, respectively. Trovafloxacin remained bactericidal against strains of *E. coli*, *S. aureus*, and *S. pneumoniae* that were exposed to growth inhibitory levels of chloramphenicol, a protein synthesis inhibitor. In contrast, chloramphenicol markedly antagonized the bactericidal activity of trovafloxacin against three isolates of *Enterococcus faecalis* (18). These results suggest that like ofloxacin, trovafloxacin exhibits the additional mechanism B in its bactericidal action against certain microorganisms.

B. Antimicrobial Spectrum of Activity

The data presented in this section summarizes all of the preclinical microbiology results available for trovafloxacin. The data is compiled from over 40 publications, abstracts, or project reports sent to the sponsor from independent investigators. The susceptibility data in Tables 1-6 are presented for each species in terms of the Minimum Inhibitory Concentration (MIC) range, MIC_{90} range, and median MIC_{90} for all available studies. The sponsor has defined the MIC as the lowest concentration of drug that inhibits the visible growth of an organism in tests run under National Committee for Clinical Laboratory Standards (NCCLS) conditions (31,32)

For comparative purposes, the susceptibility values for trovafloxacin is presented along with those for ciprofloxacin, ofloxacin, and sparfloxacin. The *in vitro* data for 15,648 clinical isolates were obtained from widely diverse locations including the United States, Europe, South Africa, and the Middle East. The susceptibility data presented in Tables 1 through 6, are organized according to the clinical indications that are proposed for trovafloxacin and the most common organisms that can be associated with these indications. The antimicrobial activity of trovafloxacin against multiply resistant organisms such as penicillin-resistant *S. pneumoniae*, enterococci, *S. aureus*, *P. aeruginosa*, and mycobacteria is given in Table 28.

The overall conclusions in this susceptibility section point to the broad spectrum of trovafloxacin including gram-positive and gram-negative aerobic, fastidious, and anaerobic organisms.

Trovafloxacin has good activity against gram-positive species and anaerobes as compared to other fluoroquinolones. Trovafloxacin is less active than ciprofloxacin or sparfloxacin against members of the *Enterobacteriaceae*. Trovafloxacin is more active than ciprofloxacin and as active as sparfloxacin against some species such as *Staphylococcus aureus* and *Neisseria gonorrhoeae* that show reduced susceptibility to ciprofloxacin. Against other isolates with reduced susceptibility to ciprofloxacin such as *Pseudomonas aeruginosa* or *Stenotrophomonas maltophilia*, trovafloxacin appears to have no potency advantage over ciprofloxacin. Against multi-resistant enterococci, trovafloxacin like other fluoroquinolones examined, has no activity.

1. Antimicrobial Activity of Trovafloxacin Against Organisms Associated with Respiratory Infections

a. Upper Respiratory Tract

i. Sinusitis

The *in vitro* activity of trovafloxacin against four bacterial species that are often associated with sinusitis are compared with that of ciprofloxacin, ofloxacin, and sparfloxacin in Table 1. The MIC range observed with trovafloxacin against 1,867 penicillin-susceptible isolates of *Streptococcus pneumoniae* was The upper range observed in this group for ciprofloxacin, ofloxacin, and sparfloxacin was 8 μg/mL, indicating that strains exist in nature which are resistant to these agents. The MIC_{90} range for trovafloxacin was for these isolates of pneumococci reported from nineteen separate studies. According to the median MIC_{90} values for Penicillin-susceptible *Streptococcus pneumoniae* (Table 1), trovafloxacin is 16, 32, and 4-fold more potent than ciprofloxacin, ofloxacin, and sparfloxacin, respectively.

This degree of potency for trovafloxacin is maintained against 498 strains of penicillin-resistant *Streptococcus pneumoniae* reported from five separate studies. The MIC_{90} range for trovafloxacin against penicillin-resistant *Streptococcus pneumoniae* was and the most resistant isolates in this group had MIC of 0.25 μg/mL. The median MIC_{90} for trovafloxacin against penicillin-resistant *Streptococcus pneumoniae* was 16, 32, and 10-fold lower than that observed for ciprofloxacin, ofloxacin, and sparfloxacin, respectively.

Trovafloxacin is also very active *in vitro* against clinical isolates of *Moraxella catarrhalis* and *Haemophilus influenzae*. The MIC_{90} range for trovafloxacin against 403 isolates of *H. influenzae*, reported from ten separate studies, was . The median MIC_{90}s for trovafloxacin and the other fluoroquinolones tested were similar at . This degree of potency was also demonstrated against 304 strains of *M. catarrhalis*, reported from nine separate studies, where the MIC_{90} range and median MIC_{90} values for trovafloxacin were and 0.03 μg/mL, respectively. At the median MIC_{90}, the potency of trovafloxacin is similar to that of sparfloxacin, ciprofloxacin, and ofloxacin.

Strains of methicillin-resistant (MRSA) or susceptible (MSSA) *Staphylococcus aureus* can also cause sinusitis. The data in Table 1 show that trovafloxacin is active against MSSA, with an MIC_{90} range of and a median MIC_{90} of 0.06 µg/mL for 666 isolates reported from thirteen studies. The MIC_{90} range of ciprofloxacin was and the median MIC_{90} was 0.75 µg/mL, indicating that trovafloxacin is about tenfold more potent than ciprofloxacin against this group. In considering the full MIC ranges reported in these studies, it is clear that some isolates of MSSA exist which appear resistant (MIC ≥4 µg/mL) to trovafloxacin, ciprofloxacin, ofloxacin, or sparfloxacin.

All four fluoroquinolones were less active *in vitro* against MRSA. The MIC range of trovafloxacin was for 487 isolates of MRSA reported from sixteen separate studies. The upper MIC range for the other three fluoroquinolones were from The median MIC_{90} s were 2.0, >16, 16, and 8 µg/mL for trovafloxacin, ciprofloxacin, ofloxacin, and sparfloxacin, respectively. Trovafloxacin like the other fluoroquinolones, has marginal activity against MRSA. The relative activity of trovafloxacin against laboratory strains of *S. aureus* with characterized mutations conferring quinolone resistance will be described in section II.H. (Table 12).

b. Lower Respiratory Tract

i. Acute Bacterial Exacerbation of Chronic Bronchitis

The organisms associated with acute bacterial exacerbation of chronic bronchitis are the same as the ones associated with sinusitis, including *S. pneumoniae* (both penicillin-susceptible and penicillin-resistant strains), *H. influenzae*, *M. catarrhalis*, and *S. aureus*. Trovafloxacin is active against the same spectrum of susceptible microorganisms as those associated with sinusitis. Data on the antimicrobial activity of trovafloxacin and other fluoroquinolones against these organisms is shown in Table 1. The description for the relative potency of trovafloxacin is the same as that given in the previous section on sinusitis.

ii. Community Acquired Pneumonia

The *in vitro* activity of trovafloxacin against 5,492 bacteria that can be associated with community acquired pneumonia has been compared with that of ciprofloxacin, ofloxacin, and sparfloxacin. Data for the isolates of *S. pneumoniae* (including penicillin-susceptible and resistant strains), *H. influenzae*, *M. catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *S. aureus*, and *Legionella pneumophila* obtained from several studies are found in Table 1. The comparative MIC_{90} results for trovafloxacin and the other fluoroquinolones for *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *S. aureus* have been described in section II.B.1.a.i. for sinusitis.

The activity of trovafloxacin against 50 isolates of *M. pneumoniae* has been described in two studies. The data in Table 1 indicate that the MIC range for trovafloxacin against these isolates is The MIC_{90} range for trovafloxacin was compared with values of 1.0, 1.0, and 0.25 µg/mL for ciprofloxacin, ofloxacin, and sparfloxacin, respectively.

This indicates that trovafloxacin is as active as sparfloxacin and about fourfold more active than either ciprofloxacin or ofloxacin against *M. pneumoniae*.

The activity of trovafloxacin against *C. pneumoniae* is described in one study. In this report, the activity of trovafloxacin against 13 isolates was equivalent to that of ofloxacin, with an MIC_{90} of 1.0 μg/mL. Despite the small size of the study one may conclude that trovafloxacin has a borderline questionable activity against *C. pneumoniae.*

Table 1. Antimicrobial Activity of Trovafloxacin and Other Fluoroquinolones Against Organisms Associated with Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis, and Community Acquired Pneumonia.

Organism	No. Isolates	Compound	MIC Range (μg/mL)	MIC_{90} Range (μg/mL)	Median MIC_{90} (μg/mL)	References
Streptococcus pneumoniae pen-S[a]	1,867	Trovafloxacin			0.125	11,33-50
	1,847	Ciprofloxacin			2.0	11,34-50
	1,427	Ofloxacin			4.0	11,36,38,39,43,45,46,48-50
	541	Sparfloxacin			0.5	11,34,36,37,39,42-45,47-50
Streptococcus pneumoniae pen-R[b]	498	Trovafloxacin			0.125	11,43,44,46,49
	498	Ciprofloxacin			2.0	11,43,44,46,49
	343	Ofloxacin			4.0	43,46,49
	306	Sparfloxacin			1.25	43,44
Haemophilus influenzae	403	Trovafloxacin			0.015	11,35-42,47
	403	Ciprofloxacin			0.015	11,35-42,47
	67	Ofloxacin			0.023	38,51
	150	Sparfloxacin			0.015	11,37,39,42,47
Moraxella catarrhalis	304	Trovafloxacin			0.03	11,35,37-40,42,47,51
	304	Ciprofloxacin			0.06	11,35,37-40,42,47,51
	53	Ofloxacin			0.075	38,51
	131	Sparfloxacin			0.031	11,37,39,42,47
Staphylococcus aureus MSSA[c]	666	Trovafloxacin			0.06	11,33-41,51-53,98
	646	Ciprofloxacin			0.75	11,34-41,51-53,98
	194	Ofloxacin			0.5	35,36,38,51,53
	130	Sparfloxacin			0.125	11,34,36,37,39
Staphylococcus aureus MRSA[d] CRSA[e]	487	Trovafloxacin			2.0	33-42,47,51-54,98
	452	Ciprofloxacin			>16	34,40,47,51-54,98
	134	Ofloxacin			16	35-36,38,51,53
	102	Sparfloxacin			8	34,36-37,39,42
Chlamydia pneumoniae	13	Trovafloxacin			1.0	57
	13	Ofloxacin			1.0	57
Mycoplasma pneumoniae	50	Trovafloxacin			0.185	38,55
	10	Ciprofloxacin			1.0	38
	50	Ofloxacin			1.0	38,55
	40	Sparfloxacin			0.25	55
Legionella pneumophila	148	Trovafloxacin			0.008	35,38,56
	133	Ciprofloxacin			0.038	35,38
	148	Ofloxacin			0.032	35,38,56

[a] Penicillin-susceptible, MIC≤0.05 μg/mL.
[b] Penicillin-resistant, MIC≥0.5 μg/mL.
[c] Methicillin-susceptible *S. aureus*.
[d] Methicillin-resistant *S. aureus*.
[e] Ciprofloxacin-resistant *S. aureus*.

Trovafloxacin's activity against 148 isolates of *L. pneumophila* was determined in three separate studies (Table 1). The MIC_{90} ranges for trovafloxacin, ciprofloxacin and ofloxacin were . The median MIC_{90} values for trovafloxacin, ciprofloxacin and ofloxacin were 0.008, 0.038, and 0.032 µg/mL, respectively. These data indicate that Trovafloxacin is as active as ciprofloxacin or ofloxacin against *L. pneumophila*.

iii. Nosocomial Pneumonia

The *in vitro* antibacterial activity of trovafloxacin has been compared with that of ciprofloxacin, ofloxacin, and sparfloxacin in studies with 6,198 bacterial isolates that can be associated with nosocomial pneumonia. Comparative susceptibility data with *S. pneumoniae*, *S. aureus* (MRSA and MSSA) and *H. influenzae* were discussed in section II.B.1.a.i. when describing sinusitis. In addition to these organisms, data for *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Enterococcus faecalis, Serratia marcescens, Morganella morganii,* and *Stenotrophomonas maltophilia* are shown in Table 2.

The antimicrobial activity of trovafloxacin was evaluated against 476 isolates of *E. coli* in eleven separate studies. The MIC range for trovafloxacin was somewhat inferior to that for ciprofloxacin, ofloxacin, and sparfloxacin . The MIC_{90} range for trovafloxacin was for ciprofloxacin, ofloxacin, and sparfloxacin respectively. The upper range for trovafloxacin was higher than that observed for ciprofloxacin, ofloxacin, and sparfloxacin. The median MIC_{90}s were similar for all four fluoroquinolones . The data from 331 *K. pneumoniae* gathered from eight separate studies indicates that trovafloxacin is slightly more active than ciprofloxacin and ofloxacin, but less active than sparfloxacin. Here, the MIC_{90} range for trovafloxacin was 0.06-1.0 µg/mL, with a median of 0.125 µg/mL. Corresponding values for ciprofloxacin, ofloxacin, and sparfloxacin were and 0.06 µg/mL; 1.0 µg/mL; 0.125 µg/mL respectively. Against 242 strains of *E. cloacae* from eight separate studies, the MIC_{90} range for trovafloxacin was compared with values of ciprofloxacin, ofloxacin, and sparfloxacin, respectively. The relative order of potency as judged by median MIC_{90} values was sparfloxacin (0.085 µg/mL), ciprofloxacin (0.312 µg/mL), trovafloxacin (1.6 µg/mL), and ofloxacin (2.12 µg/mL). For 298 strains of *P. mirabilis* in ten studies, the MIC_{90} ranged for trovafloxacin. Against *P. mirabilis*, ciprofloxacin with an MIC_{90} range and ofloxacin with an MIC_{90} range of were about four- and sixteen-fold more potent than trovafloxacin respectively. The median MIC_{90}s for trovafloxacin, ciprofloxacin, ofloxacin, and sparfloxacin were 0.5, 0.06, 0.125, and 0.5 µg/mL, respectively. Trovafloxacin was as active as ciprofloxacin, ofloxacin, and sparfloxacin against 195 *M. morganii* isolates, with an MIC_{90} range of 0.125 to 2.0 µg/mL and a median MIC_{90} of 0.5 µg/mL. Corresponding values for ciprofloxacin, ofloxacin, and sparfloxacin were
respectively.

All of the fluoroquinolones studied were inactive against *P. aeruginosa*. The MIC ranges were broad for all four compounds, with a range for trovafloxacin . The MIC_{90} ranges were also similar for all four compounds with a range reported for trovafloxacin when a total of 566 isolates were tested in eleven studies. The median MIC_{90}

values for trovafloxacin, ciprofloxacin, ofloxacin, and sparfloxacin were 2.0, 2.0, >8.0, and 2.0 µg/mL, respectively.
This inactivity was also observed with strains of *S. marcescens* and *S. maltophilia*. In tests with 211 isolates of *S. marcescens* from 9 studies, the MIC range for trovafloxacin was and the MIC_{90} values ranged from . The median MIC_{90} was 2.5 µg/mL which was similar to that observed for ofloxacin. The relative order of potency as judged by median MIC_{90} values was sparfloxacin (0.5 µg/mL), ciprofloxacin (1.0 µg/mL), ofloxacin (2.25 µg/mL), and trovafloxacin (2.5 µg/mL. All four fluoroquinolones were also inactive against 227 strains of *S. maltophilia* reported in seven studies. The MIC_{90} of trovafloxacin ranged between 0.5 and >8 µg/mL, while the median MIC_{90} was 2.0 µg/mL. Corresponding values for ciprofloxacin, ofloxacin, and sparfloxacin were and >8 µg/mL; >8.0 µg/mL; , respectively. Sparfloxacin seems to be more active than the other three fluoroquinolones.

With 574 Vancomycin-susceptible *E. faecalis* isolates reported from sixteen studies, trovafloxacin had an MIC_{90} range of This was compared with MIC_{90} ranges of for ciprofloxacin, ofloxacin, and sparfloxacin, respectively. The median MIC_{90}s for trovafloxacin, ciprofloxacin, ofloxacin, and sparfloxacin were 2.0, 2.0, 4.0, and 1.0 µg/mL, respectively. Sparfloxacin is twice as active as trovafloxacin against Van-S *E. faecalis*.

In general, trovafloxacin has moderately greater *in vitro* activity than ciprofloxacin, ofloxacin, and sparfloxacin against some Gram-positive organisms that can be associated with nosocomial pneumonia such as penicillin-susceptible and penicillin-resistant *S. pneumoniae*, methicillin susceptible *S. aureus*, and vancomycin-susceptible *Enterococcus faecalis*. Trovafloxacin is almost comparable in potency to ciprofloxacin against commonly isolated *Enterobacteriaceae* (*E. coli*, *P. mirabilis*, *K. pneumoniae*, and *M. morganii*) and MIC_{90} studies suggest that the majority of these strains will be in the susceptible range for trovafloxacin (≤1 µg/mL). Like ciprofloxacin, ofloxacin, and sparfloxacin, trovafloxacin is inactive against *P. aeruginosa*, *S. marcescens*, and *S. maltophilia*. This suggests that combination chemotherapy with a fluoroquinolone and another agent would be required in treating nosocomial pneumonia with these organisms.

Table 2. Antimicrobial Activity of Trovafloxacin and Other Fluoroquinolones Against Organisms Associated with Nosocomial Pneumonia

Organism	No. Isolates	Compound	MIC Range (μg/mL)	MIC_{90} Range (μg/mL)	Median MIC_{90} (μg/mL)	References
Escherichia coli	476	Trovafloxacin			0.06	11,35-39,41-42,47,51,53
	476	Ciprofloxacin			0.062	11,35-39,41-42,47,51,53
	193	Ofloxacin			0.125	35-36,38,51,53
	188	Sparfloxacin			0.062	11,36-37,39,42
Klebsiella pneumoniae	331	Trovafloxacin			0.125	11,35-36,39,41-42,47,53
	331	Ciprofloxacin			0.06	11,35-36,39,41-42,47,53
	95	Ofloxacin			1.0	36,39,53
	141	Sparfloxacin			0.125	11,36,39,42
Enterobacter cloacae	242	Trovafloxacin			1.6	11,35-36,39,41-42,51,53
	242	Ciprofloxacin			0.312	11,35-36,39,41-42,51,53
	90	Ofloxacin			2.12	35-36,51,53
	135	Sparfloxacin			0.085	11,36,39,42
Proteus mirabilis	298	Trovafloxacin			0.5	11,35-37,39,41-42,47,51,53
	298	Ciprofloxacin			0.06	11,35-37,39,41-42,47,51,53
	80	Ofloxacin			0.125	35,36,51,53
	166	Sparfloxacin			0.5	11,36-37,39,42
Pseudomonas aeruginosa	566	Trovafloxacin			2.0	11,35-39,41,51,53,58-59
	566	Ciprofloxacin			2.0	11,35-39,41,51,53,58-59
	357	Ofloxacin			>8	35-36,38,51,53,58-59
	256	Sparfloxacin			2.0	11,36-37,39,58
Haemophilus influenzae	403	Trovafloxacin			0.015	11,35-42,47
	403	Ciprofloxacin			0.015	11,35-42,47
	67	Ofloxacin			0.023	38,51
	150	Sparfloxacin			0.015	11,37,39,42,47
Staphylococcus aureus	487	Trovafloxacin			2.0	33-42,47,51-54,98
MRSA[d]	452	Ciprofloxacin			>16	34-42,47,51-54,98
MSSA[e]	134	Ofloxacin			16	35-36,38,51,53
	102	Sparfloxacin			8	34,36-37,39,42
Streptococcus pneumoniae	1,867	Trovafloxacin			0.125	11,33-50
Pen-S[a]	1,847	Ciprofloxacin			2.0	11,34-50
	1,427	Ofloxacin			4.0	11,36,38,43,45,46,48-50
	541	Sparfloxacin			0.5	11,34,36,37,39,42-45,47,50
Streptococcus pneumoniae	498	Trovafloxacin			0.125	11,43,44,46,49
Pen-R[b]	498	Ciprofloxacin			2.0	11,43,44,46,49
	343	Ofloxacin			4.0	43,46,49
	306	Sparfloxacin			1.25	43,44
Enterococcus faecalis	574	Trovafloxacin			2.0	11,33-41,47,51-53,59,107
Van-S[f]	537	Ciprofloxacin			2.0	11,34-41,47,51-53
	188	Ofloxacin			4.0	35-36,38,51,53
	89	Sparfloxacin			1.0	11,34,36,37,39

Organism	No. Isolates	Compound	MIC Range (µg/mL)	MIC_{90} Range (µg/mL)	Median MIC_{90} (µg/mL)	References
Serratia marcescens	211	Trovafloxacin			2.5	11,35-36,39,41,47,51,53
	211	Ciprofloxacin			1.0	11,35-36,39,41,47,51,53
	100	Ofloxacin			2.25	35-36,51,53
	91	Sparfloxacin			0.5	11,36,39
Morganella morganii	195	Trovafloxacin			0.5	11,35-37,39,41,47,51,53
	195	Ciprofloxacin			0.125	11,35-37,39,41,47,51,53
	46	Ofloxacin			0.19	35-36,51,53
	93	Sparfloxacin			1.0	11,36,37,39,53
Stenotrophomonas maltophilia	227	Trovafloxacin			2.0	35-37,39,53,58, 59
	227	Ciprofloxacin			>8	35-37,39,53,58
	197	Ofloxacin			>8	35,36,53,58-59
	142	Sparfloxacin			2.0	36,37,39,58

[a] Penicillin-susceptible, MIC≤0.05 µg/mL.
[b] Penicillin-resistant, MIC≥0.5 µg/mL.
[c] Methicillin-susceptible *S. aureus*.
[d] Methicillin-resistant *S. aureus*.
[e] Ciprofloxacin-resistant *S. aureus*.
[f] Vancomycin-susceptible *E. faecalis*

2. Antimicrobial Activity of Trovafloxacin Against Organisms Associated with Complicated and Uncomplicated Skin and Skin Structure Infections

a. Uncomplicated Skin and Skin Structure Infections

The *in vitro* activity of trovafloxacin against organisms associated with uncomplicated skin and skin structure infections is summarized in Table 3. The comparative activity of trovafloxacin against *S. aureus* (both MRSA and MSSA) was discussed in section II.B.1.a.i. under sinusitis. The activity of trovafloxacin against 118 isolates of methicillin-resistant *S. epidermidis* (MRSE) isolated in four different studies is depicted in Table 3. The MIC_{90} range with trovafloxacin for MRSE was , while that for ciprofloxacin, ofloxacin, and sparfloxacin was The median MIC_{90}s for trovafloxacin, ciprofloxacin, ofloxacin, and sparfloxacin were 2.5, >16, >16, and 8 µg/mL, respectively. This data indicate that all four fluoroquinolones are equally ineffective against MRSE isolated.

Trovafloxacin was slightly more active than the other three fluoroquinolones tested against 242 strains of *S. pyogenes* in ten different studies. The MIC_{90} range for trovafloxacin was 0.06-0.5 µg/mL against *S. pyogenes*. The MIC_{90} range for ciprofloxacin, ofloxacin, and sparfloxacin was Against 246 strains of viridans streptococci tested in 8 separate studies, trovafloxacin was moderately more active than the other three fluoroquinolones. The median MIC_{90} for trovafloxacin, sparfloxacin, ciprofloxacin, and ofloxacin were 0.25, 1.0, 4.0, and 6.0, respectively against viridans streptococci.

b. Complicated Skin and Skin Structure Infections

In addition to the Gram-positive organisms mentioned for uncomplicated skin and skin structure infections, several members of the *Enterobacteriaceae*, nonfermenter, and anaerobe groups can be associated with this disease. The comparative antimicrobial activity of trovafloxacin against *E. coli, E. cloacae, K. pneumoniae, M. morganii, P. mirabilis, Pseudomonas aeruginosa,* and *Serratia marcescens* was discussed in section II.B.1.b.iii. under nosocomial pneumonia. Other organisms in Table 3 of this section include *Providencia stuartii, Proteus vulgaris, K. oxytoca, Acinetobacter baumanii, C. freundii, Bacteroides fragilis,* and peptostreptococci.

Against 40 strains of *P. stuartii* in three studies, the MIC_{90} range for trovafloxacin, ciprofloxacin, ofloxacin, and sparfloxacin are The median MIC_{90} s for trovafloxacin, ciprofloxacin, ofloxacin, and sparfloxacin are 2.0, 0.25, 5.0, and 1.0 µg/mL. Trovafloxacin while more active than ofloxacin, it was less active than ciprofloxacin and sparfloxacin against *P. stuartii*. The MIC_{90} for trovafloxacin against 89 strains of *P. vulgaris* in six studies ranged , compared with for ciprofloxacin; , for ofloxacin; and. 0.5 µg/mL for sparfloxacin. As judged by median MIC_{90}s, trovafloxacin while less active than ciprofloxacin and ofloxacin, it was as active as sparfloxacin against *P. vulgaris*.

None of the three fluoroquinolones studied were active against the 30 strains of *A. baumanii* used in a single study, giving median MIC_{90} values >8 µg/mL for each.

Trovafloxacin was as active as the other three fluoroquinolones against *K. oxytoca*, and *Citrobacter freundii* with median MIC_{90} of 0.155 and 0.375 µg/mL respectively.

Table 3. Antimicrobial Activity of Trovafloxacin and Other Fluoroquinolones Against Organisms Associated with Complicated and Uncomplicated Skin and Skin Structure, Uncomplicated and Complicated Urinary Tract Infections, and Prostatitis.

Organism	No. Isolates	Compound	MIC Range (µg/mL)	MIC_{90} Range (µg/mL)	Median MIC_{90} (µg/mL)	References
Staphylococcus aureus (MRSA[a] and (MSSA[b]	487	Trovafloxacin			2.0	33-42,47-51,54-98
	452	Ciprofloxacin			>16	34-42,47,51-54,98
	134	Ofloxacin			16	35-36,38,51,53
	102	Sparfloxacin			8	34,36-37,39,42
Staphylococcus epidermidis (MRSE[c]	118	Trovafloxacin			2.5	35-36,53,98
	118	Ciprofloxacin			>16	35-36,53,98
	55	Ofloxacin			>16	35-36,53
	10	Sparfloxacin			8	36
Streptococcus pyogenes	242	Trovafloxacin			0.125	11,34-37,39-41,51-52
	90	Sparfloxacin			0.5	11,34,36,37,39
	242	Ciprofloxacin			0.75	11,34-37,39-41,51-52
	35	Ofloxacin			1.5	36,51
viridans	246	Trovafloxacin			0.25	33-34,36,38-40,47,52

Organism	No. Isolates	Compound	MIC Range (μg/mL)	MIC_{90} Range (μg/mL)	Median MIC_{90} (μg/mL)	References
streptococci	226	Ciprofloxacin			4.0	34,36,38-40,47,52
	55	Ofloxacin			6.0	36,38
	56	Sparfloxacin			1.0	34,36,39
Escherichia coli	476	Trovafloxacin			0.06	11,35-39,41-42,47,51,53
	476	Ciprofloxacin			0.062	11,35-39,41-42,47,51,53
	193	Ofloxacin			0.125	35-36,38,51,53
	188	Sparfloxacin			0.062	11,36-37,39,42
Enterobacter cloacae	242	Trovafloxacin			1.6	11,35-36,39,41-42,51,53,11,36,39,42
	135	Sparfloxacin			0.085	
	242	Ciprofloxacin			0.312	11,35-36,39,41-42,51,53
	90	Ofloxacin			2.12	35-36,51,53
Klebsiella oxytoca	94	Trovafloxacin			0.155	11,35-36,39
	94	Ciprofloxacin			0.06	11,35-36,39
	36	Ofloxacin			0.185	35-36
	83	Sparfloxacin			0.25	11,36,39
Citrobacter freundii	123	Trovafloxacin			0.375	11,35-36,39,51,53
	123	Ciprofloxacin			0.125	11,35-36,39,51,53
	75	Ofloxacin			1.0	35-36,51,53
	63	Sparfloxacin			0.25	11,36,39
Proteus mirabilis	298	Trovafloxacin			0.5	11,35-37,39,41-42,47,51,53
	298	Ciprofloxacin			0.06	11,35-37,39,41-42,47,51,53
	80	Ofloxacin			0.125	35,36,51,53
	166	Sparfloxacin			0.5	11,36-37,39,42
Pseudomonas aeruginosa	566	Trovafloxacin			2.0	11,35-39,41,51,53,58-59
	256	Sparfloxacin			2.0	11,36-37,39,58
	566	Ciprofloxacin			2.0	11,35-39,41,51,53,58-59
	357	Ofloxacin			>8	35-36,38,51,53,58-59
Klebsiella pneumoniae	331	Trovafloxacin			0.125	11,35-36,39,41-42,47,53
	141	Sparfloxacin			0.125	11,36,39,42
	331	Ciprofloxacin			0.06	11,35-36,39,41-42,47,53
	95	Ofloxacin			1.0	36,39,53
Morganella morganii	195	Trovafloxacin			0.5	11,35-37,39,41,47,51,53
	93	Sparfloxacin			1.0	11,36,37,39,53
	195	Ciprofloxacin			0.125	11,35-37,39,41,47,51,53
	46	Ofloxacin			0.19	35-36,51,53
Serratia marcescens	211	Trovafloxacin			2.5	11,35-36,39,41,47,51,53
	91	Sparfloxacin			0.5	11,36,39
	211	Ciprofloxacin			1.0	11,35-36,39,41,47,51,53
	100	Ofloxacin			2.25	35-36,51,53
Providencia stuartii	40	Trovafloxacin			2.0	35,39,51
	40	Ciprofloxacin			0.25	35,39,51
	20	Ofloxacin			5.0	35,51
	20	Sparfloxacin			1.0	39

Organism	No. Isolates	Compound	MIC Range (µg/mL)	MIC_{90} Range (µg/mL)	Median MIC_{90} (µg/mL)	References
Proteus vulgaris	89	Trovafloxacin			0.5	35,37,39,47,51,53
	38	Sparfloxacin			0.5	37,39
	89	Ciprofloxacin			0.03	35,37,39,47,51,53
	30	Ofloxacin			0.125	35,51,53
Acinetobacter baumanii	30	Trovafloxacin			>8	30
	30	Ciprofloxacin			>8	30
	30	Ofloxacin			>8	30
Bacteroides fragilis	1,404	Trovafloxacin			0.5	11,37-39,60-67
	515	Metronidazole			1.28	11,60-62,64,66
	1,339	Ciprofloxacin			16.0	11,37,39,60-64,66-67
	874	Ofloxacin			16.0	38,62-63,66
Peptostreptococci	156	Trovafloxacin			1.0	38,60-61,66
	156	Ciprofloxacin			4.0	38,60-61,66
	55	Ofloxacin			12.0	38,66
	123	Metronidazole			1.0	60-61
Streptococcus agalactiae	120	Trovafloxacin			0.25	34-37,39,41,51
	120	Ciprofloxacin			2.0	34-37,39,41,51
	40	Ofloxacin			2.0	36-51
	56	Sparfloxacin			0.75	34,36,37,39
Enterococcus faecalis	574	Trovafloxacin			2.0	11,33-41,47,51-53,59,107
	537	Ciprofloxacin			2.0	11,33-41,47,51-53
Van-S[d]	188	Ofloxacin			4.0	35-36,38,51,53
	89	Sparfloxacin			1.0	11,34,36,37,39

[a] Methicillin-susceptible *S. aureus*.
[b] Methicillin-resistant *S. aureus*.
[c] Methicillin-resistant *S. epidermidis*
[d] Vancomycin-susceptible *E. faecalis*

Trovafloxacin has improved activity over the other fluoroquinolones studied against 1,404 isolates of *B. fragilis* in 12 separate studies. The MIC_{90} range for trovafloxacin was compared with for ciprofloxacin and for ofloxacin. The median MIC_{90}s for trovafloxacin, ciprofloxacin, and ofloxacin were 0.5, 16.0, and 16.0 µg/mL, respectively. Trovafloxacin was also active against 156 isolates of peptostreptococci in four studies, with an MIC range Trovafloxacin was 4 to 8-fold more active than ciprofloxacin against this group when the MIC_{90} ranges and median MIC_{90}s are considered. Trovafloxacin was as active as metronidazole against *B. fragilis* and peptostreptococci as judged by median MIC_{90}s.

3. Antimicrobial Activity of Trovafloxacin Against Organisms Associated with Uncomplicated Urinary Tract Infections

Uncomplicated urinary tract infection (cystitis) can be associated with infection by *E. coli*, *Klebsiella* spp., other Enterobacteriaceae, *S. saprophyticus, P. mirabilis, P. aeruginosa*, enterococci, *Acinetobacter* spp., *Alcaligenes* spp., *Citrobacter* spp., *Gardnerella vaginalis*, beta-hemolytic streptococci, and *Neisseria gonorrhoeae*.

The antimicrobial activity of trovafloxacin compared with ciprofloxacin, ofloxacin, and sparfloxacin against organisms that can be associated with these infections is given in Table 3. The relative antimicrobial activity of trovafloxacin against most of these organisms has been discussed in sections II.B.1. and II.B.2. nosocomial pneumonia and skin/skin structure infections. In addition, the activity of trovafloxacin against isolates of *S. agalactiae* is shown in Table 3. Trovafloxacin had an MIC_{90} range of against 120 isolates of this species reported from seven studies. Trovafloxacin was as active as sparfloxacin and eightfold more active than ciprofloxacin and ofloxacin at the median MIC_{90}.

The median MIC_{90} values of trovafloxacin would not support its use in urinary tract infections due to *P. aeruginosa* or *E. cloacae*.

4. Antimicrobial Activity of Trovafloxacin Against Organisms Associated with Prostatitis

Development of prostatitis has been associated with infection of the prostate by *E. coli*. The antimicrobial activity of trovafloxacin against isolates of *E. coli* is shown in Table 3 and the comparative activity was discussed in Section II.B.1.b.iii. nosocomial pneumonia.

5. Antimicrobial Activity of Trovafloxacin Against Organisms Associated with Acute, Uncomplicated Urethral, Cervical and Pharyngeal Gonorrhea

The antimicrobial activity of trovafloxacin compared with that of ciprofloxacin, ofloxacin, and sparfloxacin against *Neisseria gonorrhoeae* is shown in Table 4. In studies with 509 clinical isolates from six different investigators, the MIC range for trovafloxacin was The MIC_{90} range was and the median MIC_{90} was 0.006 µg/mL. Trovafloxacin was comparable in potency to ciprofloxacin and ofloxacin and less potent than sparfloxacin against *N.*

gonorrhoeae. The median MIC_{90} for ofloxacin was 0.03 µg/mL and that for sparfloxacin was 0.0028 µg/mL.

Table 4. Antimicrobial Activity of Trovafloxacin and Other Fluoroquinolones Against *Neisseria gonorrhoeae*

Organism	No. Isolates	Compound	MIC Range (µg/mL)	MIC_{90} Range (µg/mL)	Median MIC_{90} (µg/mL)	References
Neisseria gonorrhoeae	509	Trovafloxacin			0.006	11,35,37-38,68-69
	509	Ciprofloxacin			0.008	11,35,37-38,68-69
	295	Ofloxacin			0.03	38,68
	70	Sparfloxacin			0.0028	11,37

6. Antimicrobial Activity of Trovafloxacin Against Organisms Associated with Pelvic Inflammatory Disease

Pelvic inflammatory disease is a serious illness that can be associated with infection by *N. gonorrhoeae* and *Chlamydia trachomatis*. The comparative antimicrobial activity of trovafloxacin against gonococci is given in Table 4 and discussed in section II.B.5. on acute, uncomplicated gonorrhea. *Chlamydia trachomatis* is discussed below.

7. Antimicrobial Activity of Trovafloxacin Against Organisms Associated with Nongonococcal Urethritis and Cervicitis

Nongonococcal urethritis and cervicitis can be associated with infection by *Chlamydia trachomatis*. The activity of trovafloxacin and ofloxacin were evaluated in one study with 19 organisms (70). The MIC ranges were respectively. The MIC_{90} for trovafloxacin was 0.05 µg/mL compared to 1.0 µg/mL for ofloxacin.

8. Antimicrobial Activity of Trovafloxacin Against Organisms Associated with Acute Pelvic Infections

Acute pelvic infections in adult females can be associated with a mixed etiology of microorganisms. *E. coli, E. cloacae, K. pneumoniae, E. faecalis, S. agalactiae,* Peptostreptococcus, *Prevotella* spp., and *Staphylococcus* spp. can be associated with these infections. The antimicrobial activity of trovafloxacin against these organisms is shown in Table 5. This group of organisms is contained within those that cause complicated skin and skin structure infections, complicated intraabdominal or urinary tract infections, and are discussed in sections (II.B.2., II.B.3. and II.B.8.).

Table 5. Antimicrobial Activity of Trovafloxacin and Other Fluoroquinolones Against Organisms Associated with Acute Pelvic Infections

Organism	No. Isolates	Compound	MIC Range (μg/mL)	MIC Range (μg/mL)	Median MIC_{90} (μg/mL)	References
Escherichia coli	476	Trovafloxacin			0.06	11,35-39,41-42,47,51,53
	476	Ciprofloxacin			0.062	11,35-39,41-42,47,51,52
	193	Ofloxacin			0.125	35-36,38,51,53
	188	Sparfloxacin			0.062	11,36-37,39,42
Klebsiella pneumoniae	331	Trovafloxacin			0.125	11,35-36,39,41-42,47,53
	141	Sparfloxacin			0.125	11,36,39,42
	331	Ciprofloxacin			0.06	11,35-36,39,41-42,47,53
	95	Ofloxacin			1.0	36,39,53
Enterobacter cloacae	242	Trovafloxacin			1.6	11,35-36,39,41-42,51,53
	135	Sparfloxacin			0.085	11,36,39,42
	242	Ciprofloxacin			0.312	11,35-36,39,41-42,51,53
	90	Ofloxacin			2.12	35-36,51,53
Pseudomonas aeruginosa	566	Trovafloxacin			2.0	11,35-39,41,51,53,58-59
	256	Sparfloxacin			2.0	11,36-37,39,58
	566	Ciprofloxacin			2.0	11,35-39,41,51,53,58-59
	357	Ofloxacin			>8	35-36,38,51,53,58-59
Staphylococcus aureus	487	Trovafloxacin			2.0	33-42,47,51-54,98
(MRSA)	102	Sparfloxacin			8	34,36-37,39,42
(MSSA)	452	Ciprofloxacin			>16	34-42,47,51-54,98
	134	Ofloxacin			16	35-36,38,51,53
E. faecalis (Van-S)	574	Trovafloxacin			2.0	11,33-41,47,51-53,59, 107
	537	Ciprofloxacin			2.0	11,34-41,47,51-53
	188	Ofloxacin			4.0	35-36,38,51,53
	89	Sparfloxacin			1.0	11,34,36,37,39
Streptococcus agalactiae	120	Trovafloxacin			0.25	34-37,39,41,51
	120	Ciprofloxacin			2.0	34-37,39,41,51
	40	Ofloxacin			2.0	36-51
	56	Sparfloxacin			0.75	34,36,37,39
Prevotella bivia	118	Trovafloxacin			1.5	60,65,66
	101	Ciprofloxacin			32	60,66
	50	Ofloxacin			16	66
	101	Metronidazole			2.5	60,66
Peptostreptococci	156	Trovafloxacin			1.0	38,60-61,66
	156	Ciprofloxacin			4.0	38,60-61,66
	55	Ofloxacin			12.0	38,66
	123	Metronidazole			1.0	60-61
Prevotella intermedia	27	Trovafloxacin			1.0	60,62
	27	Ciprofloxacin			8.25	60,62
	13	Ofloxacin			0.5	62
	27	Metronidazole			2.25	60,62

9. Antimicrobial Activity of Trovafloxacin Against Organisms Associated with Complicated Intraabdominal Infections

Intraabdominal infections, like complicated skin structure or acute pelvic infections, can have a mixed etiology. Such infections are often the result of surgery and other trauma. Thus, these infections can involve a mixture of aerobic Gram-positive organisms, *Enterobacteriaceae*, nonfermenters, and a diverse group of anaerobes. The antimicrobial activity of trovafloxacin against many of these organisms (*E. coli, Enterobacter cloacae, K. pneumoniae,* viridans streptococci, enterococci, and *S. aureus*) is given in Table 6. The comparative activity of trovafloxacin against this group of bacteria is discussed in section II.B.2. complicated skin and skin structure infections. In addition, a more extensive list of enterococci is given in Table 6. In fifteen studies with *E. faecalis*, trovafloxacin had an MIC_{90} range of against 574 vancomycin-susceptible isolates. This was compared with MIC_{90} ranges of for ciprofloxacin, ofloxacin, and sparfloxacin, respectively. The median MIC_{90}s for trovafloxacin, ciprofloxacin, ofloxacin, and sparfloxacin were 2.0, 2.0, 4.0, and 1.0 µg/mL, respectively. MICs for vancomycin resistant *E. faecalis* were considerably higher for all of the fluoroquinolones . This trend was also evident when data was compared from vancomycin-susceptible and -resistant isolates of *E. faecium* (Table 6). The median MIC_{90} for 285 vancomycin-resistant *E. faecium* was 8.0 µg/mL for trovafloxacin and >16 µg/mL for ciprofloxacin.

Table 6. Antimicrobial Activity of Trovafloxacin and Other Agents Against Organisms That can be Associated with Intraabdominal Infections

Organism	No. Isolates	Compound	MIC Range (μg/mL)	MIC_{90} Range (μg/mL)	Median MIC_{90} (μg/mL)	References
Escherichia coli	476	Trovafloxacin			0.06	11,35-39,41-42,47,51,53
	476	Ciprofloxacin			0.062	11,35-39,41-42,47, 51,53
	193	Ofloxacin			0.125	35-36,38,51,53
	188	Sparfloxacin			0.062	11,36-37,39,42
Enterobacter cloacae	242	Trovafloxacin			1.6	11,35-36,39,41-42,51,53
	242	Ciprofloxacin			0.312	11,35-36,39,41-42,51,53
	90	Ofloxacin			2.12	35-36,51,53
	135	Sparfloxacin			0.085	11,36,39,42
Klebsiella pneumoniae	331	Trovafloxacin			0.125	11,35-36,39,41-42,47,53
	331	Ciprofloxacin			0.06	11,35-36,39,41-42,47,53
	95	Ofloxacin			1.0	36,39,53
	141	Sparfloxacin			0.125	11,36,39,42
Staphylococcus aureus (MSSA)[a] and (MRSA)[b]	487	Trovafloxacin			2.0	33-42,47,51 54,98
	452	Ciprofloxacin			>16	34-42,47,51-54,98
	134	Ofloxacin			16	35-36,38,51,53
	102	Sparfloxacin			8	34,36-37,39,42
Viridans streptococci	246	Trovafloxacin			0.25	33-34,36,38-40,47,52
	226	Ciprofloxacin			4.0	34,36,38-40,47,52
	55	Ofloxacin			6.0	36,38
	56	Sparfloxacin			1.0	34,36,39
E. faecalis (Van-S)[c]	574	Trovafloxacin			2.0	11,33-41,47,51-53,59,107
	537	Ciprofloxacin			2.0	11,34-41,47,51-53
	188	Ofloxacin			4.0	35-36,38,51,53
	89	Sparfloxacin			1.0	11,34,36,37,39
E. faecalis (Van-R)[d]	33	Trovafloxacin			8	33,67,97,107
	19	Ciprofloxacin			16	67,97
	12	Ofloxacin			>8	67
	19	Sparfloxacin			>16	67,97
E. faecium (Van-S)	130	Trovafloxacin			2.0	33,35,37,39,40,51,52,107
	110	Ciprofloxacin			4.0	35,37,39,40,51,52
	20	Ofloxacin			6.0	35,51
	23	Sparfloxacin			1.0	37,39
E. faecium (Van-R)	285	Trovafloxacin			8.0	33,34,36,52,53,67,97,107
	231	Ciprofloxacin			>16	34,36,52,53,67,97
	150	Ofloxacin			>16	36,53,67
	195	Sparfloxacin			>10	34,36,67,97

Organism	No. Isolates	Compound	MIC Range (μg/mL)	MIC_{90} Range (μg/mL)	Median MIC_{90} (μg/mL)	References
Bacteroides fragilis	1,404	Trovafloxacin			0.5	11,37-39,60-67
	1,339	Ciprofloxacin			16.0	11,37,39,60-64,66-67
	874	Ofloxacin			16.0	38,62-63,66
	515	Metronidazole			1.28	11,60-62,64,66
Bacteroides thetaiotaomicron	361	Trovafloxacin			1.0	60,62-64,66
	361	Ciprofloxacin			32	60,62-64,66
	238	Ofloxacin			64	62-63,66
	159	Metronidazole			1.25	60,62,64,66
B. ovatus	218	Trovafloxacin			2.0	60,62-64,66
	218	Ciprofloxacin			64	60,62-64,66
	135	Ofloxacin			64	62-63,66
	100	Metronidazole			1.25	60,62,64,66
B. distasonsis	245	Trovafloxacin			1.0	60,62-64,66
	245	Ciprofloxacin			32.0	60,62-64,66
	173	Ofloxacin			16.0	62,63,66
	127	Metronidazole			1.5	60,62,64,66
B. vulgatus	150	Trovafloxacin			4.0	60,62-64,66
	150	Ciprofloxacin			64	60,62-64,66
	105	Ofloxacin			64	62,63,66
	95	Metronidazole			1.0	60,62,64,66
B. uniformis	74	Trovafloxacin			4.0	62-64,66
	74	Ciprofloxacin			40	62-64,66
	58	Ofloxacin			64	62-63,66
	54	Metronidazole			1.0	62,64,66
B. fragilis Group	2,018	Trovafloxacin			1.0	60-61,63-65
	723	Ciprofloxacin			32.0	60-61,64
	723	Metronidazole			2.0	60-61,64
Clostridium perfringens	179	Trovafloxacin			0.25	38,60-62,65-66
	161	Ciprofloxacin			0.5	38,60-62
	121	Ofloxacin			0.5	38,62,66
	109	Metronidazole			1.5	60-62,66
C. difficile	71	Trovafloxacin			1.0	38,60-62
	71	Ciprofloxacin			8.0	38,60-62
	44	Ofloxacin			8.0	38,62
	41	Metronidazole			0.25	60-62
Prevotella bivia	118	Trovafloxacin			1.0	60,65,66
	101	Ciprofloxacin			32.0	60,66
	50	Ofloxacin			16.0	66
	101	Metronidazole			2.5	60,66

Organism	No. Isolates	Compound	MIC Range (μg/mL)	MIC_{90} Range (μg/mL)	Median MIC_{90} (μg/mL)	References
P. intermedia	27	Trovafloxacin			1.0	60,62
	27	Ciprofloxacin			8.25	60,62
	13	Ofloxacin			0.5	62
	27	Metronidazole			2.25	60,62
Prevotella melaninogenica	21	Trovafloxacin			1.5	60,66
	21	Ciprofloxacin			16.0	60
	10	Ofloxacin			64.0	66
	21	Metronidazole			2.25	60,66
Prevotella sp.	126	Trovafloxacin			1.0	38,61-62,66
	126	Ciprofloxacin			12.0	38,61-62,66
	77	Ofloxacin			16.0	38,62,66
	101	Metronidazole			1.0	61-62,66
Fusobacterium nucleatum	68	Trovafloxacin			0.375	60-62,66
	68	Ciprofloxacin			2.0	60-62,66
	29	Ofloxacin			3.0	62,66
	68	Metronidazole			0.25	60-62,66
Peptostreptococci	156	Trovafloxacin			1.0	38,60-61,66
	156	Ciprofloxacin			4.0	38,60-61,66
	55	Ofloxacin			12.0	38,66
	123	Metronidazole			1.0	60-61,66

[a] Methicillin-susceptible *S. aureus*.
[b] Methicillin-resistant *S. aureus*.
[c] Vancomycin-susceptible.
[d] Vancomycin-resistant.

The activity of trovafloxacin against an extensive list of anaerobic pathogens is also given in Table 6. Unlike ciprofloxacin and ofloxacin, trovafloxacin inhibits the majority of anaerobe species with a median MIC_{90} ≤1.0 μg/mL. A total of 1,404 isolates of *Bacteroides fragilis* were tested in twelve separate studies. The MIC_{90} range for trovafloxacin was compared with MIC_{90} ranges for ciprofloxacin, ofloxacin, and metronidazole of μg/mL, respectively. When considering the median MIC_{90}, trovafloxacin was as active as metronidazole and 32-fold more active than ciprofloxacin and ofloxacin. When considering median MIC_{90}s, trovafloxacin was also as active as metronidazole and more active than ciprofloxacin and ofloxacin against isolates of *B. thetaiotaomicron,* and *B. distasonsis* (Table 6). The median MIC_{90}s for trovafloxacin against these species in the order given are 1.0, and 1.0 μg/mL. Trovafloxacin was also tested against 2,018 strains classified in five studies as *B. fragilis* group. The trovafloxacin MIC_{90} range for these organisms was compared with for ciprofloxacin. The median MIC_{90}s for trovafloxacin, ciprofloxacin, and metronidazole were 1.0, 32.0, and 2.0 μg/mL, respectively. As judged by the median MIC_{90}s, trovafloxacin was not active against *B. ovatus, B. vulgatus,* and *B. uniformis*. The median

MIC_{90}s for trovafloxacin against these species in the order given are 2.0, 4.0, and 4.0 µg/mL as compared to metronidazole's median MIC_{90}s of 1.25, 1.0 , and 1.0 µg/mL, respectively.

Trovafloxacin is as active as ciprofloxacin, ofloxacin, and metronidazole against *Clostridium perfringens*. The MIC_{90} range against 179 isolates of *C. perfringens* tested in 6 separate studies was with a median of 0.25 µg/mL. This is compared to median MIC_{90} values for ciprofloxacin, ofloxacin, and metronidazole of 0.5, 0.5, and 1.5 µg/mL, respectively. The median MIC_{90} of trovafloxacin against *C. difficile* was 1.0 µg/mL This median value is three dilutions lower than that obtained with ciprofloxacin and ofloxacin. However, metronidazole is four folds more active against *C. difficile* than trovafloxacin. The median MIC_{90} for metronidazole against *C. difficile* is 0.25 µg/mL.

In general trovafloxacin is as active as metronidazole and more active than ciprofloxacin and ofloxacin against *Prevotella* spp. Against 126 isolates classified as *Prevotella* spp. in four separate studies, the MIC_{90} range for trovafloxacin was compared with values of for metronidazole, ciprofloxacin and ofloxacin, respectively. The median MIC_{90}s for trovafloxacin, metronidazole, ciprofloxacin and ofloxacin, against these species are 1.0, 1.0, 12.0, and 16.0 µg/mL

Trovafloxacin was also as active as metronidazole and slightly more active than ciprofloxacin or ofloxacin against *Fusobacterium nucleatum*. The median MIC_{90} for 68 isolates reported in four separate studies was 0.375, 2.0, 3.0, and 0.25 µg/mL for trovafloxacin, ciprofloxacin, ofloxacin, and metronidazole, respectively.

Trovafloxacin was as active as metronidazole and moderately more active than ciprofloxacin or ofloxacin against 156 isolates of peptostreptococci tested in four different studies. The median MIC_{90} was 1.0, 4.0, 12.0, and 1.0 µg/mL for trovafloxacin, ciprofloxacin, ofloxacin, and metronidazole, respectively.

10. Antimicrobial Activity of Trovafloxacin Against Organisms Associated with Meningitis

Bacterial meningitis in children and adults is most commonly caused by *N. meningitidis*, *S. pneumoniae*, and *H. influenzae*. The *in vitro* activity of trovafloxacin against *S. pneumoniae* (penicillin-susceptible and -resistant isolates) and *H. influenzae* has been discussed in detail in section II.B.1.a.i., sinusitis. Trovafloxacin is also highly potent against isolates of *N. meningitis*. Against 71 isolates of *N. meningitidis* tested in two studies, the MIC range for trovafloxacin was and the median MIC_{90} was 0.005 µg/mL. These values are comparable to those obtained for ciprofloxacin, ofloxacin, and sparfloxacin (see Table 7).

11. In Vitro susceptibility profile of Trovafloxacin

Trovafloxacin has been tested for *in vitro* activity against a variety of microorganisms derived from infections throughout the world. Data derived from these studies are summarized in Table 7. These studies were conducted using standardized and controlled *in vitro* susceptibility test methods. Minimum inhibitory concentrations (MICs) were determined by a dilution method,