V. CONCLUSIONS

Trovafloxacin is a new antimicrobial of the fluoronaphthyridone class. Given its chemical structure and mechanism of action against bacterial DNA gyrase and topoisomerase IV, trovafloxacin can be considered to be among the fluoroquinolone antimicrobial agents.

Trovafloxacin has an elimination half-life in humans of around 10 to 12 hours, which suggests that it can be dosed once daily for some indications. The projected dose for serious infections is 200 to 300 mg once daily. Accumulation effects of multiple oral doses (1.3-fold) produce peak blood levels of between 2.1 and 4.1 μg/mL for a 200 mg oral regimen of trovafloxacin. Peak blood levels following multiple 300 mg intravenous doses of alatrofloxacin range

Trovafloxacin is 70% bound to human serum protein which is higher than that of other fluoroquinolones. *In vitro* studies with some enteric organisms show that addition of 70% human serum to susceptibility test medium raises the MICs of trovafloxacin from 2 to 32-fold. This appears to have a minor effect on the activity of trovafloxacin, however, since efficacy in mouse protection studies paralleled the *in vitro* potency of trovafloxacin against challenge pathogens.

The elimination of trovafloxacin is predominantly by the biliary route. Less than 10% of drug is recovered intact in the urine, resulting in peak urine levels of around 4.5 μg/mL from 0-2 h following a 100 mg oral dose. Peak urine levels are around 18 μg/mL following a 300 mg dose.

Unlike several other fluoroquinolones, trovafloxacin appears to lack phototoxic activity and it does not interfere with the metabolism of theophylline. Coadministration of trovafloxacin with food does not markedly affect the extent of absorption. Age or gender differences minimally impact the pharmacokinetic profile of trovafloxacin.

Trovafloxacin seems more active than ciprofloxacin and ofloxacin and as active as sparfloxacin against some Gram-positive organisms, and anaerobes. The published susceptibility studies focused on testing the activity of trovafloxacin against *S. pneumoniae*, evaluating a number of penicillin-susceptible and -resistant isolates. The MIC range of trovafloxacin against 1,867 penicillin-susceptible pneumococci from nineteen studies The MIC_{90} range and the median MIC_{90} was 0.125 μg/mL. This degree of activity was 16, 32, and 4-fold greater than that observed with ciprofloxacin, ofloxacin, and sparfloxacin, respectively. Trovafloxacin is equally active against pneumococci that were penicillin-resistant. The MIC_{90} range for trovafloxacin against 498 penicillin-resistant isolates and the least susceptible strain had an MIC of 0.25 μg/mL. *In vitro* selection of resistance studies indicated that step-wise mutation in *grlA* (topoisomerase IV) and *gyrA* (DNA gyrase) are necessary to confer high-level resistance to ciprofloxacin (MIC $\geq$64 μg/mL) in pneumococci. Trovafloxacin is still quite active against the first-step mutants (MIC = 0.5 μg/mL), although it is not active against isolates with mutations in both genes (MIC = 8 μg/mL). Each step of mutation occurs at a low frequency of 1×10^{-9}. This low mutation frequency, coupled with the fact that resistance loci are not plasmid encoded, suggests that high-level resistance to trovafloxacin may not be widespread in *S. pneumoniae*.

Trovafloxacin is more active than ciprofloxacin against staphylococci. Strains of MSSA have an MIC_{90} range to trovafloxacin, compared with values of 0.5 to 8.0 μg/mL

for ciprofloxacin. Trovafloxacin is also active against some of MRSA that are also resistant to ciprofloxacin. The median MIC_{90}s against such isolates for trovafloxacin, ciprofloxacin, ofloxacin, and sparfloxacin were 2.0, >16, 16, and 8 μg/mL, respectively. Clearly, while trovafloxacin is active against some isolates of *S. aureus*, it is not predicted to be efficacious against isolates with MICs falling above the breakpoint of 1 μg/mL.

The activity of trovafloxacin was evaluated against 574 isolates of vancomycin-susceptible *E. faecalis*. Trovafloxacin had an MIC_{90} range compared with values of 1.0 to 32 μg/mL for ciprofloxacin. Trovafloxacin was inactive against vancomycin-resistant isolates of *E. faecalis* with an MIC_{90} range for 33 isolates. Neither trovafloxacin nor ciprofloxacin were very active against vancomycin-resistant isolates of *E. faecium*. The MIC_{90} ranges for trovafloxacin and ciprofloxacin were
respectively for 285 such isolates.

In vitro trovafloxacin is active against the group of pathogens that are associated with community acquired pneumonia. As described above, trovafloxacin is more active than ciprofloxacin, ofloxacin, and sparfloxacin against pneumococci. Trovafloxacin is as active as ciprofloxacin, ofloxacin, and sparfloxacin against isolates of *Haemophilus influenzae*, *M. catarrhalis*, *L. pneumophila*. Against *M. pneumoniae*, trovafloxacin is slightly more active than ciprofloxacin or ofloxacin and as active as sparfloxacin . The available data suggest that trovafloxacin like sparfloxacin should provide broad coverage for community acquired pneumonia, particularly given its activity against pneumococci.

The spectrum of trovafloxacin suggests that it might have clinical utility against nosocomial pneumonia pathogens given its improved *in vitro* activity against *S. pneumoniae*. Trovafloxacin has activity against members of the *Enterobacteriaceae* that is comparable to that of ciprofloxacin and sparfloxacin. Median MIC_{90} values of trovafloxacin were ≤1 μg/mL against *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *M. morganii*. Ciprofloxacin and sparfloxacin had better activity than trovafloxacin against *E. cloacae*. Median MIC_{90}s for trovafloxacin for *P. aeruginosa*, *S. marcescens*, and *S. maltophilia* were 2.0, 2.5, and 2.0 μg/mL, respectively. The latter group of organisms is generally less susceptible to fluoroquinolones, and the activity observed for trovafloxacin is similar to that of ciprofloxacin and sparfloxacin. Inspection of the data from several reports suggests that trovafloxacin is inactive against pseudomonads that have already acquired resistance to ciprofloxacin.

Trovafloxacin possesses activity against one of the organisms associated with sexually transmitted disease. It was essentially equivalent in potency to ciprofloxacin against 509 isolates of *N. gonorrhoeae* . However trovafloxacin was inferior to sparfloxacin against 70 isolates of *N. gonorrhoeae*
Trovafloxacin was active against 50 gonococci with reduced susceptibility to ciprofloxacin (ciprofloxacin MIC_{90} = 1.0 μg/mL versus trovafloxacin MIC_{90} = 0.25 μg/mL

Trovafloxacin is active against the most commonly isolated bacteria in urinary tract infections and prostatitis. Given the limited levels of drug recovered in urine it remains to be seen whether adequate coverage will be achieved with less susceptible pathogens in complicated UTI and pyelonephritis.
A slight possible advantage of trovafloxacin over ciprofloxacin and ofloxacin involves its *in vitro* activity against anaerobes. The MIC_{90} range of trovafloxacin against 1,404 isolates of *B. fragilis*

from twelve studies was At the median MIC_{90} trovafloxacin was 32 more active than ciprofloxacin against this species. During clinical trials however, of 13 isolates of *Bacteroides* spp. only 9 (69%) were eradicated (no information on clinical outcome is available). This degree of eradication seems to be in contradiction with the *in vitro* data. This degree of difference in *in vitro* activity is less visible when one considers anaerobic species such as , *C. perfringens* (trova. MIC_{90} of 0.25 verses cipro./oflox. MIC_{90} of 0.5 μg/mL), *C. difficile* (trova. MIC_{90} of 1.0 verses cipro./oflox. MIC_{90} of 8.0 μg/mL), *Fusobacterium* spp. (trova. MIC_{90} of 1.0 verses cipro. MIC_{90} of 3 μg/mL), and peptostreptococci (trova. MIC_{90} of 1.0 verses cipro. MIC_{90} of 4.0 μg/mL). During clinical trials, there were no *C. difficile* or *C. perfringens* isolated and of 24 isolates of peptostreptococci 21 (88%) were eradicated (no information on clinical outcome is available).

The available data from Phase III trials indicate that using the MIC breakpoint of $\leq$ 1.0, 2.0, and $\geq$4 μg/mL for susceptible, intermediate and resistant respectively, of 1,954 isolates, 55 (2.8%) were resistant, 28 (1.4%) were intermediate and 1871 (95.8%) were susceptible to trovafloxacin. As might be predicted, resistance was observed most frequently in isolates of enterococci, *P. aeruginosa*, and members of the *Enterobacteriaceae*. Few resistant isolates of *S. aureus*, *S. epidermidis*, and *S. haemolyticus*, Streptococci, and *Corynebacterium*, were also encountered.

VI. PACKAGE INSERT

A. Isolates Approved

The following organisms may be placed in the label. The final decision on whether or not an organism should be in the clinical efficacy list will depend on the Medical Officer's final review of this product. If the clinical picture reveals that some of these genera/species are not clinically cured, they will be deleted even though the *in vitro* results demonstrate otherwise.
Trovafloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganisms
Enterococcus faecalis (many strains are only moderately susceptible)
Staphylococcus aureus (methicillin-susceptible strains)
Staphylococcus epidermidis (methicillin-susceptible strains)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes
Viridans group streptococci

Aerobic gram-negative microorganisms
Escherichia coli
Gardnerella vaginalis
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis

Neisseria gonorrhoeae
Proteus mirabilis
Pseudomonas aeruginosa

Anaerobic microorganisms
Bacteroides fragilis
Peptostreptococcus species
Prevotella species

Other microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown.** Trovafloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of ≤ 1 µg/mL (≤ 2 µg/mL for anaerobes) against most (90%) strains of the following microorganisms; however, the safety and effectiveness of trovafloxacin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trails:

Aerobic Gram-positive microorganisms
Streptococcus pneumoniae (penicillin-resistant strains)

Aerobic Gram-negative microorganisms
Citrobacter freundii
Enterobacter aerogenes
Morganella morganii
Proteus vulgaris

Anaerobic microorganisms
Bacteroides distasonis
Bacteroides ovatus
Clostridium perfringens

Other microorganisms
Mycoplasma hominis
Ureaplasma urealyticum

B. Interpretive Criteria Established

The following MIC interpretive criteria should be used for testing non-fastidious aerobic organisms

MIC (µg/mL)	Interpretation
≤ 1.0	Susceptible (S)
2.0	Intermediate (I)
≥ 4.0	Resistant (R)

OR (see addendum by Dr. Albert Sheldon)

MIC (µg/mL)	Interpretation
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

The following zone diameter interpretive criteria should be used for testing non-fastidious aerobic organisms:

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
15-17	Intermediate (I)
≤ 14	Resistant (R)

OR (see addendum by Dr. Albert Sheldon)

Zone Diameter (mm)	Interpretation
≥ 17	Susceptible (S)
14-16	Intermediate (I)
≤ 13	Resistant (R)

The following MIC interpretive criteria should be used for testing *Haemophilus* spp.:

MIC (µg/mL)	Interpretation
≤ 1.0	Susceptible (S)

The following zone diameter interpretive criteria should be used for testing *Haemophilus* spp.:

Zone Diameter (mm)	Interpretation
≥ 22	Susceptible (S)

The following MIC interpretive criteria should be used for testing *Streptococcus* spp. including *Streptococcus pneumoniae*:

MIC (µg/mL)	Interpretation
≤ 1.0	Susceptible (S)
2.0	Intermediate (I)
≥ 4.0	Resistant (R)

The following zone diameter interpretive criteria should be used for testing *Streptococcus* spp. including *Streptococcus pneumoniae*:

Zone Diameter (mm)	Interpretation
≥ 19	Susceptible (S)
18-16	Intermediate (I)
≤ 15	Resistant (R)

The following MIC interpretive criteria should be used for testing *Neisseria gonorrhoeae*:

MIC (µg/mL)	Interpretation
≤ 0.125	Susceptible (S)
0.25	Intermediate (I)
≥ 0.5	Resistant (R)

The following zone diameter interpretive criteria should be used for testing *Neisseria gonorrhoeae*:

Zone Diameter (mm)	Interpretation
≥ 37	Susceptible (S)
34-36	Intermediate (I)
≤ 33	Resistant (R)

The following MIC interpretive criteria should be used for testing anaerobic microorganisms:

MIC (µg/mL)	Interpretation
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

SPONSOR NOTIFICATION
The sponsor should be notified of the following:

1) The following organisms which the sponsor has placed in the first list (clinical efficacy list) must be deleted (see medical officers' reviews).

Aerobic gram-positive microorganisms:
Staphylococcus aureus (methicillin and cephalosporin-resistant strains)
Staphylococcus haemolyticus
Staphylococcus hominis
Staphylococcus simulans
Streptococcus anginosus
Streptococcus equisimilis
Streptococcus pneumonia (penicillin-resistant strains)
Streptococcus species

Aerobic gram-negative microorganisms:
Enterobacter cloacae
Enterobacter species
Klebsiella oxytoca

Anaerobic microorganisms:
Bacteroides species
Bacteroides thetaiotaomicron
Corynebacterium species
Fusobacterium nucleatum
Fusobacterium species

Other microorganisms:
Gardnerella vaginalis

2) The following organisms which the sponsor has placed in the *in vitro* section of the label must be deleted:

Aerobic gram-positive microorganisms:

Bacillus cereus:	In addition to food poisoning, based on many reports and frequent and regular occurrence *Bacillus cereus* is now accepted to be associated with mild to severe, necrotic or gangrenous infected wounds. Even though the median MIC_{90} is acceptable the number of the organisms tested are very few. This organism will not be allowed in the label.
Corynebacterium jeikeium	is the most common corynebacterial pathogen isolated in the clinical laboratory. It is associated with septicemia, endocarditis skin and soft tissue infections, and occasionally, meningitis, peritonitis, and pneumonia, particularly in the compromised and previously treated host. The number of the isolates and the MIC_{90} of 2.0 μg/mL is not acceptable. This organisms will not be allowed in the label.
Enterococcus faecium (Van-S) *Enterococcus faecium* (Van-R)	Enterococci are involved most commonly in urinary tract infections and are implicated in 10% of all such infections. Intra abdominal or pelvic wound infections are the next commonly encountered infections. However, these wound cultures are frequently polymicrobial, and the role of enterococci in this setting remains controversial. Bacteremia is the third most common type of infection, and enterococci are the third leading cause of nosocomial bacteremia. Endocarditis is less common than bacteremia and enterococci is estimated to be the causative agent in 5-20% of bacterial endocarditis cases. *E. faecalis* is the most commonly encountered species in this setting, but various other species also have been implicated as causes of

	endocarditis. The MIC_{90} is above the susceptible breakpoint for both Van-R and Van-S *E. faecium*. This organism will not be allowed in the label
Staphylococcus saprophyticus	is an important opportunistic pathogen in human urinary tract infections, especially in young, sexually active females. It has been proposed as an agent of nongonococcal urethritis in males and prostatitis. Although the median MIC_{90} was 0.06 µg/mL, the number of the isolates are not sufficient to justify inclusion in the label. *Staphylococcus saprophyticus* will not be allowed in the label.

Aerobic gram-negative microorganisms:

Acinetobacter baumanii	There are few isolates and the MIC_{90} is >8.0 µg/mL. *Acinetobacter baumanii* will not be allowed in the label.
Alcaligenes faecalis	There are few isolates and the MIC_{90} is >8.0 µg/mL. *Alcaligenes faecalis* will not be allowed in the label
Alcaligenes xylosoxidans subsp. *denitrificans*	There are few isolates and the MIC_{90} is 4.0 µg/mL. *Alcaligenes xylosoxidans* subsp. *denitrificans* will not be allowed in the label
Alcaligenes xylosoxidans subsp. *xylosoxidans*	There are few isolates and the MIC_{90} is >8.0 µg/mL. *Alcaligenes xylosoxidans* subsp. *xylosoxidans* will not be allowed in the label
Bordetella bronchiseptica	There are data on very few isolates and the MIC_{90} is 1.0 µg/mL. *Bordetella bronchiseptica* will not be allowed in the label
Brevundimonas diminuta	There are data on very few isolates and the MIC_{90} is 8.0 µg/mL. *Brevundimonas diminuta* will not be allowed in the label
Burkholderia cepacia	There are data on very few isolates and the MIC_{90} is 4.0 µg/mL. *Burkholderia cepacia* will not be allowed in the label
Citrobacter diversus	Less than 100 isolates were tested in a number of different centers. However, majority of the isolates were older than 5 years. Even though the median MIC_{90} was 0.06 µg/mL and this organism may be associated with pneumonia, *Citrobacter diversus* will not be allowed into the label.
Neisseria meningitidis	is an organism that is implicated in community -acquired pneumonia, urethritis, and most importantly in meningitis. Due to the seriousness of meningococcal meningitis and the associated public health issues, this organism will be listed

	ONLY if the efficacy of a drug is studied and demonstrated in well controlled clinical trials. *Neisseria meningitidis* will not be allowed in the label.
Providencia rettgeri	There are not enough isolates tested and *Providencia rettgeri* will not be allowed into the label.
Providencia stuartii	There is not enough isolates tested and the median MIC_{90} is 2.0 μg/mL. *Providencia stuartii* will not be allowed into the label.
P. fluorescens putida	There is not enough isolates tested and *Pseudomonas fluorescens putida* will not be allowed into the label.
Pseudomonas stutzeri	There is not enough isolates tested and *Pseudomonas stutzeri* will not be allowed into the label.
Salmonella enteritidis	There is not enough isolates tested and Infectious diarrhea is not an indication for trovafloxacin. *Salmonella enteritidis* will not be allowed into the label.
Salmonella typhi	There is not enough isolates tested and Infectious diarrhea is not an indication for trovafloxacin. *Salmonella typhi* will not be allowed into the label.
Salmonella spp.	Infectious diarrhea is not an indication for trovafloxacin. *Salmonella* spp. will not be allowed into the label.
Serratia marcescens	is an important cause of extraintestinal infections, having caused many nosocomial outbreaks associated with blood transfusions surgery, and the urinary tract. Most of the MIC_{90}s were above the susceptible breakpoint. *Serratia marcescens* will not be allowed in the label.
Shigella spp.	Infectious diarrhea is not an indication for trovafloxacin. *Shigella* spp. will not be allowed into the label.
Stenotrophomonas maltophilia	is ubiquitous in nature and has also been isolated from the hospital environment. It is the third most frequently isolated nonfermentative gram-negative rod in the clinical laboratory. Strains may be colonizers (e.g., in cystic fibrosis) or infecting agents. Septicemia (often associated with intravenous catheters), pneumonia, and wound infections have been reported. Most of the isolates tested are not recent isolates and the MICs were greater than the susceptible breakpoint. The two recent studies with 50 and 30 isolates each reported the MIC_{90} to be >8.0 μg/mL and 4.0 μg/mL respectively. *Stenotrophomonas maltophilia* will not be allowed into the label.

Vibrio cholerae	There is not enough isolates tested and *Vibrio cholerae* will not be allowed into the label.
Yersinia enterocolitica	Infectious diarrhea is not an indication for trovafloxacin and there is not enough isolates tested therefore, *Yersinia enterocolitica* will not be allowed into the label.
Anaerobic microorganisms:	
Bacteroides uniformis	*Bacteroides uniformis* as a member of *Bacteroides fragilis* group is recovered from most intra-abdominal infections and may occur in infections at other sites. The MIC_{90} of 46 recent isolates was 4.0 µg/mL. *Bacteroides uniformis* will not be allowed in the label.
Clostridium difficile	*Clostridium difficile* is the major cause of antibiotic-associated diarrhea and pseudomembranous colitis. There were less than 100 isolates tested and the one U.K. study with one third of the isolates, reported the MIC_{90} to be 4.0 µg/mL. *Clostridium difficile* will not be allowed in the label.
Clostridium ramosum	There is not enough isolates tested and *Clostridium ramosum* will not be allowed into the label.
Fusobacterium mortiferum	There is no *in vitro* data presented in the NDA to support the inclusion of this organism. *Fusobacterium mortiferum* will not be allowed in the label.
Fusobacterium nucleatum	There is only 12 isolates that may be considered as "recent" isolates. The reported MIC_{90} was 0.5 µg/mL. There is not enough *in vitro* data presented to justify the inclusion of *Fusobacterium nucleatum* in the label. *Fusobacterium nucleatum* will not be allowed in the label.
Prevotella bivia	Only data for 62 isolates could be found in the NDA. One study with the majority of the isolates reported the MIC_{90} to be 2.0 µg/mL. *Prevotella bivia* will not be allowed in the label.
Prevotella intermedia	Only data for 13 isolates could be found in the NDA. There is not enough *in vitro* data presented to justify the inclusion of *Prevotella intermedia* in the label. *Prevotella intermedia* will not be allowed
Prevotella melaninogenica	Only data for 11 isolates could be found in the NDA. There is not enough *in vitro* data presented to justify the inclusion of *Prevotella melaninogenica* in the label. *Prevotella melaninogenica* will not be allowed
Other microorganisms:	
Legionella dumoffii	

Legionella micdadei *Legionella longbeacheae* *Legionella maltophilia*??	There were no *in vitro* data presented in the NDA in support of inclusion of *Legionella dumoffii, Legionella micdadei, Legionella longbeacheae,* or *Legionella maltophili*??. These organisms will not be allowed in the label.
Toxoplasma gondii	There were no *in vitro* data presented in the NDA to support the inclusion of *Toxoplasma gondii* in the label. *Toxoplasma gondii* will not be allowed in the label.

3) Reword the "Microbiology" section to read **exactly** as indicated bellow.

Trovafloxacin is a fluoronaphthyridone related to the fluoroquinolones with *in vitro* activity against a wide range of gram-negative and gram-positive aerobic, and anaerobic microorganisms. The bactericidal action of trovafloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. Mechanism of action of fluoroquinolones including trovafloxacin is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore, fluoroquinolones may be active against pathogens that are resistant to these antibiotics. There is no cross-resistance between trovafloxacin and the mentioned classes of antibiotics. The overall results obtained from *in vitro* synergy studies, testing combinations of trovafloxacin with beta-lactams and aminoglycosides, indicate that synergy is strain specific and not commonly encountered. This agrees with results obtained previously with other fluoroquinolones. Resistance to trovafloxacin *in vitro* develops slowly via multiple-step mutation in a manner similar to other fluoroquinolones. Resistance to trovafloxacin *in vitro* occurs at a general frequency of between Although cross-resistance has been observed between trovafloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to trovafloxacin.

Trovafloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganisms
Enterococcus faecalis (many strains are only moderately susceptible)
Staphylococcus aureus (methicillin-susceptible strains)
Staphylococcus epidermidis (methicillin-susceptible strains)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes
Viridans group streptococci

Aerobic gram-negative microorganisms
Escherichia coli
Gardnerella vaginalis
Haemophilus influenzae

Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Neisseria gonorrhoeae
Proteus mirabilis
Pseudomonas aeruginosa

Anaerobic microorganisms
Bacteroides fragilis
Peptostreptococcus species
Prevotella species

Other microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown.**

Trovafloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of ≤ 2 µg/mL against most (90%) strains of the following microorganisms; however, the safety and effectiveness of trovafloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive microorganisms
Streptococcus pneumoniae (penicillin-resistant strains)

Aerobic Gram-negative microorganisms
Citrobacter freundii
Enterobacter aerogenes
Morganella morganii
Proteus vulgaris

Anaerobic microorganisms
Bacteroides distasonis
Bacteroides ovatus
Clostridium perfringens

Other microorganisms
Mycoplasma hominis
Ureaplasma urealyticum

NOTE: *Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare* complex organisms are commonly resistant to trovafloxacin.

NOTE: The activity of trovafloxacin against *Treponema pallidum* has not been evaluated; however, other quinolones are not active against *Treponema pallidum*. (See WARNINGS.)

Susceptibility Tests:

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of trovafloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing non-fastidious aerobic organisms

MIC (µg/mL)	Interpretation
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

For testing *Haemophilus* spp.[a]:

MIC (µg/mL)	Interpretation[b]
≤ 1.0	Susceptible (S)

[a] These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using Haemophilus Test Medium (HTM)[1]

[b] The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* spp. including *Streptococcus pneumoniae*[c]:

MIC (µg/mL)	Interpretation
≤ 1.0	Susceptible (S)
2.0	Intermediate (I)
≥ 4.0	Resistant (R)

[c] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2 - 5 % lysed horse blood.

For testing *Neisseria gonorrhoeae*[d]:

MIC (μg/mL)	Interpretation
≤ 0.125	Susceptible (S)
0.25	Intermediate (I)
≥ 0.5	Resistant (R)

[d] These interpretive standards are applicable to agar dilution tests with GC agar base and 1% defined growth supplement[1].

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected. Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard trovafloxacin powder should provide the following MIC values:

Microorganism	MIC Range (μg/mL)
Escherichia coli ATCC 25922	0.004-0.016
S. aureus ATCC 29213	0.008-0.03
P. aeruginosa ATCC 27853	0.25-2.0
E. faecalis ATCC 29212	0.06-0.25
Haemophilus influenzae[e] ATCC 49247	0.004-0.016
S. pneumoniae[f] ATCC 49619	0.06-0.25
N. gonorrhoeae[g] ATCC 49226	0.004-0.016

[e] This quality control range is applicable to only *H. influenzae* ATCC 49247

[f] This quality control range is applicable to only *S. pneumoniae* ATCC 49619

[g] This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 μg trovafloxacin to test the susceptibility of microorganisms to trovafloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10-μg trovafloxacin disk should be interpreted according to the following criteria:

The following zone diameter interpretive criteria should be used for testing non-fastidious aerobic organisms:

Zone Diameter (mm)	Interpretation
≥ 17	Susceptible (S)
14-16	Intermediate (I)
≤ 13	Resistant (R)

For testing *Haemophilus* spp.[h]:

Zone Diameter (mm)	Interpretation[i]
≥ 22	Susceptible (S)

h. These zone diameter standards are applicable only to tests with *Haemophilus* spp

i. The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* spp. including *Streptococcus pneumoniae*[j]:

Zone Diameter (mm)	Interpretation
≥ 19	Susceptible (S)
18-16	Intermediate (I)
≤ 15	Resistant (R)

j. These zone diameter standards only apply to tests performed

For testing *Neisseria gonorrhoeae*[k]:

Zone Diameter (mm)	Interpretation
≥ 37	Susceptible (S)
34-36	Intermediate (I)
≤ 33	Resistant (R)

k. These interpretive standards are applicable to disk diffusion tests with GC agar base and 1% defined growth supplement[2] incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for trovafloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 10-µg trovafloxacin disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter Range (mm)
Escherichia coli ATCC 25922	29-36
S. aureus ATCC 25923	29-35
P. aeruginosa ATCC 27853	21-27
Haemophilus influenzae[l] ATCC 49247	32-39
S. pneumoniae[m] ATCC 49619	25-32
N. gonorrhoeae[n] ATCC 49226	42-55

l. This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49247

m. This quality control range is applicable only to tests performed by disk diffusion

n. This quality control range is only applicable to tests performed by disk diffusion

Anaerobic techniques: For anaerobic bacteria, the susceptibility to trovafloxacin as MICs can be determined by standardized test methods[3]. The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

Interpretation is identical to that stated above for results using dilution techniques.

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized trovafloxacin powder should provide the following MIC values:

Microorganism	MIC[p] (µg/mL)
Bacteroides fragilis ATCC 25285	0.125-0.5
Bacteroides thetaiotaomicron ATCC 29741	0.25-1.0
Eubacterium lentum ATCC 43055	0.25-1.0

p. These quality control ranges were derived from tests performed

References:

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically--Fourth Edition; Approved Standard, NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Villanova, PA, January, 1997.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests--Sixth Edition; Approved Standard, NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Villanova, PA, January 1997.
3. National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria--Third Edition; Approved Standard, NCCLS Document M11-A3, Vol. 13, No. 26, NCCLS, Villanova, PA, December, 1993.

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BIBLIOGRAPHY

1. Sutcliffe, J.A., Gootz, T.D., Barrett, J.F. (1989). Biochemical characteristics and physiological significance of major DNA topoisomerases. *Antimicrob. Agents Chemother.* **33**, 2027-2033.

2. Gootz, T.D., Brighty, K.E. (1996). Fluoroquinolone antibacterials: SAR, mechanism of action, resistance and clinical aspects. *Med. Res. Revs.* **16**, 433-486.

3. Lewis, R.J., Tsai, F.T.F., Wigley, D.B. (1996). Molecular mechanisms of drug inhibition of DNA gyrase. *Bio Essays.* **18**, 661-671.

4. Maxwell, A. (1992). The molecular basis of quinolone action. *J. Antimicrob. Chemother.* **30**, 409-414.

5. Willmott, C.J.R., Critchlow, S.E., Eperon, I.C., Maxwell, A. (1994). The complex of DNA gyrase and quinolone drugs with DNA forms a barrier to transcription by RNA polymerase. *Journal of Molecular Biology* **242**, 351-363.

6. Peng, H., Marians, K.J. (1993). *Escherichia coli* topoisomerase IV. *The Journal of Biological Chemistry* **268**, 24481-24490.

7. Kato, J-i., Nishimura, Y., Imamura, R., Niki, H., Hiraga, S., Suzuki, H. (1990). New topoisomerase essential for chromosome segregation in *E. coli*. *Cell* **63**, 393-404.

8. Hoshino, K., Kitamura, A., Morrissey, I., Sato, K., Kato, J-I., Ikeda, H. (1994). Comparison of inhibition of *Escherichia coli* topoisomerase IV by quinolones with DNA gyrase inhibition. *Antimicrobial Agents and Chemotherapy* **38**, 2623-2627.

9. Ferrero, L., Cameron, B., Manse, B., Lagneaux, D., Crouzet, J., Famechon, A., Blanche, F. (1994). Cloning and primary structure of *Staphylococcus aureus* DNA topoisomerase IV: a primary target of fluoroquinolones. *Mol. Microbiol.* **13**, 641-653.

10. Ferrero, L., Cameron, B., Crouzet, J. (1995). Analysis of *gyrA* and *grlA* mutations in stepwise-selected ciprofloxacin-resistant mutants of *Staphylococcus aureus*. *Antimicrobial Agents and Chemotherapy* **39**, 1554-1558.

11. Gootz, T.D., Brighty, K.E., Anderson, M.R., Schmieder, B.J., Haskell, S.L., Sutcliffe, J.A., Castaldi, M.J., McGuirk, P.R. (1994). *In vitro* activity of CP-99,219, a novel 7-(3-azabicyclo[3.1.0]hexyl) naphthyridone antimicrobial. *Diagnostic Microbiology and Infectious Disease* **19**, 235-243.

12. Brighty, K.E., Gootz, T.D. (1997). The chemistry and biological profile of trovafloxacin. *J. Antimicrob. Chemother.* (Suppl.) in-press.

13. Gootz, T.D., Zaniewski, R., Haskell, S., Schmieder, B., Tankovic, J., Girard, D., Couravalin, P., Polzer, R.J. (1996). Activity of the new fluoroquinolone trovafloxacin

(CP-99,219) against DNA gyrase and topoisomerase IV mutants of *Streptococcus pneumoniae* selected *in vitro*. *Antimicrob. Agents Chemother.* 40: 2691-2697.

14. Lewin, C.S., Smith, J.T. (1988). Bactericidal mechanisms of ofloxacin. *J. Antimicrob. Chemother.* **22** (Suppl. C), 1-8.

15. Lewin, C.S., Morrissey, I., Smith, J.T. (1991). The mode of action of quinolones: 6 – the paradox in activity of low and high concentrations and activity in the anaerobic environment. *Eur. J. Clin. Microbiol. and Infect. Dis.* **10**, 240-248.

16. Lewin, C.S., Amyes, S.G.B. (1990). Bactericidal action of PD-127,391, an enhanced spectrum quinolone. *J. Med. Microbiol.* **33**, 67-70.

17. Ratcliffe, N.T., Smith, J.T. (1985). Norfloxacin has a novel bactericidal mechanism unrelated to that of other 4-quinolones. *J. Pharm. Pharmacol.* **37**, Suppl. 92P.

18. Morrissey, I. (1996). Bactericidal activity of trovafloxacin (CP-99,219), an azabicyclo-naphthyridone antibacterial-quinolone analogue. *Journal of Antimicrobial Chemotherapy,* (in press).

19. Courtright, J.B., Turowski, D.A., Sonstein, S.A. (1988). Alteration of bacterial DNA structure, gene expression, and plasmid encoded antibiotic resistance following exposure to enoxacin. *J. Antimicrob. Chemother.* **21** (Suppl. B), 1-18.

20. Trucksis, M., Wolfson, J.S., Hooper, D.C. (1991). A novel locus conferring fluoroquinolone resistance in *Staphylococcus aureus*. *J. Bacteriol.* **173**, 5854-5860.

21. Teng, R., Liston, T.E., Harris, S.C. (1996). Multiple-dose pharmacokinetics and safety of trovafloxacin in healthy volunteers. *Journal of Antimicrobial Chemotherapy* **37**, 955-963.

22. Teng, R., Vincent J., Baris, B., Willavize, S. (1995). Pharmacokinetics of single and multiple intravenous doses of CP-116,517, the prodrug of CP-99,219 in healthy male volunteers. Abstract F240, 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, Sept. 17-20.

23. Teng, R., Dogolo, L.C., Willavize, S.A., Vincent, J. (1995). Effect of food on the bioavailability of CP-99,219, a new fluoroquinolone antibiotic, in healthy male volunteers. *Can. J. Infect. Dis.* **6** (Suppl. C):445C.

24. Teng, R., Dogolo, L.C., Willavize, S.A., Vincent, J. (1995). Effects of maalox and omeprazole on the bioavailability of CP-99,219, a new quinolone antibiotic, in healthy male volunteers. *Can. J. Infect. Dis.* **6** (Suppl. C):445C.

25. Vincent, J., Teng, R., Dogolo, L.C., Willavize, S.A. (1995). Effect of steady-state CP-99,219 on the pharmacokinetics of single and multiple doses of theophylline in healthy male volunteers. In *Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California*. Abstract F239, p. 155. American Society for Microbiology, Washington, DC.

26. Wise, R., Mortiboy, D., Child, J., Andrews, J.M. (1996). Pharmacokinetics and penetration into inflammatory fluid of trovafloxacin (CP-99,219). *Antimicrob. Agents Chemother.* **40**, 47-49.

27. Mann, H.J., Bitterman, P.B., Anderson, A.C., Teng, R., Johnson, A., Avery, M., Vincent, J. (1995). CP-99,219 penetration into human bronchial tissues and fluids following the Administration of a single dose. In *Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California.* Abstract F241, p. 155. American Society for Microbiology, Washington, DC.

28. Dalvie, D., Navetta, K., Khosla, N. (1994). Excretion and metabolism of a new quinolone antibiotic, CP-99,219, in Sprague-Dawley rats and beagle dogs. In *Proceedings of the Sixth North American ISSX Meeting, Raleigh, North Carolina.* Abstract 223, p. 223. International Society of Study of Xenobiotics.

29. Teng, R., Harris, S.C., Nix, D.E., Schentag, J.J., Foulds, G., Liston, T.E. (1995). Pharmacokinetics and safety of trovafloxacin (CP-99,219), a new quinolone antibiotic, following administration of single oral doses to healthy male volunteers. *Journal of Antimicrobial Chemotherapy* **36**, 385-394.

30. Teng, R., Dogolo, L.C., Willavize, S.A., Vincent, J. (1995). Effect of age and gender on the pharmacokinetics of CP-99,219, a new quinolone antibiotic, in healthy volunteers. In *Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California.* Abstract F238, p. 154. American Society for Microbiology, Washington, DC.

31. National Committee for Clinical Laboratory Standards (1990). Approved standard M7-A3. *Standard methods for dilution antimicrobiol susceptibility tests for bacteria that grow aerobically.* National Committee for Clinical Laboratory Standards, Villanova, PA.

32. National Committee for Clinical Laboratory Standards (1993). *Methods for antimicrobiol susceptibility testing of anaerobic bacteria. Approved Standard M11-A3.* NCCLS, Villanova, PA.

33. Shonekan, D., Handwerger, S., Mildvan, D. (1996). Comparative *in vitro* activities of RP59500 (quinupristin/dalfopristin), CL 329,998, CL 331,002, CP-99,219, clinafloxacin, (CI-960, PD - 127, 391) teicoplanin and vancomycin against Gram-positive bacteria. *Antimicrobial Agents and Chemotherapy*, submitted.

34. Eliopoulos, G.M., Klimm, K., Eliopoulos, C.T., Ferraro, M.J., Moellering, R.C., Jr. (1993). *In vitro* activity of CP-99,219, a new fluoroquinolone, against clinical isolates of Gram-positive bacteria. *Antimicrobial Agents and Chemotherapy* **37**, 366-370.

35. Briggs Gooding, B., Jones, R.N. (1993). *In vitro* antimicrobial activity of CP-99,219, a novel azabicyclo-naphthyridone. *Antimicrobial Agents and Chemotherapy* **37**, 349-353.

36. Rolston, K.V.I., Ho, D.H., LeBlanc, B., Streeter, H., Dvorak, T. (1996). *In vitro* activity of CP-99,219, a novel investigational azabicyclo-naphthyridone, against clinical bacterial isolates from patients with cancer. *Journal of Antimicrobial Chemotherapy* (Suppl.), submitted.

37. Child, J., Andrews, J., Boswell, F., Brenwald, N., Wise, R. (1995). The *in vitro* activity of CP-99,219, a new naphthyridone antimicrobial agent: a comparison with fluoroquinolone agents. *Journal of Antimicrobial Chemotherapy* **35**; 869-876.

38. Felmingham, D., Robbins, M.J., Ingley, K., Mathias, I., Bhogal, H., Leakey, A., Ridgway, G.L., Grüneberg, R.N. (1996). *In vitro* activity of trovafloxacin (CP-99,219), a new fluoroquinolone, against recent clinical isolates. *Journal of Antimicrobial Chemotherapy*, in press.

39. Neu, H.C., Chin, N. (1994). *In vitro* activity of the new fluoroquinolone CP-99,219. *Antimicrobial Agents and Chemotherapy* **38**, 2615-2622.

40. Sefton, A.M., Maskell, J.P., Rafay, A.M., Whiley, A., Williams, J.D. (1997). The *in vitro* activity of trovafloxacin a new fluoroquinolone against Gram-positive bacteria. *Journal of Antimicrobial Chemotherapy*, in press.

41. Cunha, B.A., Hussain Qadri, S.M., Ueno, Y., Walters, E.A., Domenico, P. (1996). Antibacterial activity of trovafloxacin (CP-99,219) against nosocomial Gram-positive and Gram-negative isolates. *Journal of Antimicrobial Chemotherapy* Suppl., in press.

42. Crokaert, F., Aoun, M., Duchateau, V., Grenier, P., Rossi, C., Vandermies, A., Klastersky, J. (1996). *In vitro* activity of CP-99,219, in comparison with other quinolones. *In Abstracts of the 7th European Congress of Clinical Microbiology and Infectious Diseases, Vienna, Austria.* Abstract 732, p. 142.

43. Klugman, K., Wasas, A. (1995). *In vitro* activity of the fluoroquinolone trovafloxacin against penicillin-susceptible and -resistant *Streptococcus pneumoniae*. *Journal of Antimicrobial Chemotherapy* **36**, 873-874.

44. Urbásková, P., Trupl, J., Hupková, H., Appelbaum, P.C., Jacobs, M.R. (1996). *In vitro* susceptibility of pneumococci to trovafloxacin, penicillin G, and other antimicrobial agents in the Czech Republic and Slovakia. *Eur. J. Clin. Microbiol. Infect. Dis.* **15**: 686-688.

45. Pankuch, G.A., Jacobs, M.R., Appelbaum, P.C. (1995). Activity of CP-99,219 compared with DU-6859a, ciprofloxacin, ofloxacin, levofloxacin, lomefloxacin, tosulfloxacin, sparfloxacin, and grepafloxacin against penicillin-susceptible and -resistant pneumococci. *J. Antimicrob. Chemother.* **35**, 230-232.

46. Olsson-Liljequist, B., Hoffman, B.M., Hedlund, J. (1996). Activity of trovafloxacin against blood isolates of *Streptococcus pneumoniae* in Sweden. *Eur. J. Clin. Microbiol. Infect. Dis.* **15**: 671-675.

47. Verbist, L., Verhaegen, J. (1996). *In vitro* activity of trovafloxacin versus ciprofloxacin against clinical isolates. *Eur. J. Clin. Microbiol. Infect. Dis.* **15**: 683-685.

48. Thomson, K.S., Chartrand, S.A., Sanders, C.C., Block, S.L. (1996). Trovafloxacin, a new fluoroquinolone with potent activity against *Streptococcus pneumoniae*. *Antimicrob. Agents Chemother.* (in press).

49. Fuchs, P.C., Barry, A.L., Brown, S.D. (1996). Tentative interpretive criteria for testing the susceptibility of *Streptococcus pneumoniae* to eight fluoroquinolones. *Antimicrob. Agents Chemother.* (in press).

50. Kocagoz, S., Gui, D., Unal, S., Akalin, H.E. (1995). *In vitro* activity of CP-99,219 against clinical isolates. Abstr. F231, 35th Interscience Conference on Antimicrobiol Agents Chemother. 17-20 September, San Francisco, CA.

51. Fuchs, P.C., Barry, A.L., Brown, S.D., Sewell, D.L. (1996). *In vitro* activity and selection of disk content for disk diffusion susceptibility tests with trovafloxacin. *Eur. J. Clin. Microbiol. Infect. Dis.* **15**: 678-682.

52. Coque, T.M., Singh, K.V., Murray, B.E. (1996). Comparative *in vitro* activity of the new Fluoroquinolone trovafloxacin (CP-99,219) against Gram-positive cocci. *Journal of Antimicrobial Chemotherapy* **37**: 1011-1016.

53. Dembry, L.M., Farrell, P.A., Orcutt, D.R., Gerrity, L.A., Andriole, V.T. (1996). *In vitro* activity of trovafloxacin (CP-99,219) against sensitive and resistant aerobic bacteria using the standard microdilution broth method and E-test. *J. Antimicrob. Chemother.* (Suppl.) in press.

54. Jones, R.N. (1995). *In vitro* antimicrobial activity of CP-99,219, a new 7-azabicyclonaphthyridone. *Drugs* **49**, (Suppl. 21): 205-207.

55. Kenny, G.E., Cartwright, F.D. (1996). Susceptibilities of *Mycoplasma pneumoniae*, *Mycoplasma hominis* and *Ureaplasma urealyticum* to a new quinolone, Trovafloxacin (CP-99,219). Antimicrob. *Agents Chemother.* **40**: 1048-1049.

56. Edelstein, P.H., Edelstein, M.A.C., Ren, J., Polzer, R., Gladue, R.P. (1996). Activity of trovafloxacin (CP-99,219) against *Legionella* isolates: *in vitro* activity, intracellular accumulation and killing in macrophages, and pharmacokinetics and treatment of guinea pigs with *L. pneumophila* pneumonia. *Antimicrobial Agents and Chemotherapy* **40**, 314-319.

58. Visalli, M.A., Bajaksouzian, S., Jacobs, M.R., Appelbaum, P.C. (1996). Activity of trovafloxacin alone and combined with ceftazidime, imipenem and amikacin against Gram-negative non-fermenters. *Abstract E87 36th Interscience Conference on Antimicrobial Agents and Chemotherapy*, New Orleans, LA, Sept. 15-18.

59. Fass, R.J., Barnishan, J., Solomon, M.C., Ayers, L.W. (1996). *In vitro* activities of quinolones, B-Lactams, Tobramycin and trimethoprim-sulfamethoxazole against nonfermentative gram-negative bacilli. *Antimicrobial Agents and Chemotherapy* **40**: 1412-1418.

60. Spangler, S.K., Jacobs, M.R., Appelbaum, P.C. (1994). Activity of CP-99,219 compared with those of ciprofloxacin, grepafloxacin, metronidazole, cefoxitin, piperacillin, and piperacillin-tazobactam against 489 anaerobes. *Antimicrobial Agents and Chemotherapy* **38**, 2471-2476.

61. Wexler, H.M., Molitoris, E., Molitoris, D., Finegold, S.M. (1996). *In vitro* activities of trovafloxacin against 557 strains of anaerobic bacteria. *Antimicrob. Agents Chemother.* **40**: 2232-2235.

62. Bowker, K.E., Wootton, M., Holt, H.A., Reeves, D.S., MacGowan, A.P. (1996). The *in vitro* activity of trovafloxacin and nine other antimicrobials against 413 anaerobic bacteria (J. Antimicrob. Chemother. 38: 271-281.

63. Snydman, D.R., McDermott, L. (1996). Analysis of the *in vitro* activity of trovafloxacin (CP-99,219) against *Bacteroides* species. *Infect. Dis. in Clin. Prac.* 5: (3 Suppl.): S96-S100.

64. Aldridge, K.E., Ashcraft, D. (1995). Comparison of the *in vitro* activity of CP-99,219 to that of ciprofloxacin and other antimicrobials against clinical strains of the *Bacteroides fragilis* group. Abstract F232, 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, Sept. 17-20, San Francisco, CA.

65. Barry, A.L., Fuchs, P.C., Thornsberry, C., McLaughlin, J.C., Jenkins, S.G., Hardy, D.J., Allen, S.D. (1996). Methods of measuring susceptibility of anaerobic bacteria to trovafloxacin, including quality control parameters. *Eur. J. Clin. Microbiol. Infect. Dis.* **15**: 676-678.

66. Hecht, D.W., Osmolski, J.R. (1996). Activity of trovafloxacin (CP-99,219) compared with five other agents against 585 anaerobes using three media (submitted for publication).

67. Cormican, M., Jones, R. (1996). *In vitro* antimicrobial activity of trovafloxacin (CP-99,219) tested by two methods against 150 vancomycin-resistant enterococcal isolates. *J. Antimicrob. Chemothe. 37: 847-849.*

68. Knapp, J.S., Neal, S.W., Parekh, M.C., Rice, R.J. (1995). *In vitro* activity of a new fluoroquinolone, CP-99,219, against strains of *Neisseria gonorrhoeae. Antimicrobial Agents and Chemotherapy* **39**, 987-989.

69. van Rijsoort-Vos, J.H., Stolz, E., Verbrugh, H.A., Kluytmans, J.A.J.W. (1995). *In vitro* activity of a new quinolone (CP-99,219) compared with ciprofloxacin, pefloxacin, azithromycin, and penicillin against *Neisseria gonorrhoeae. J. Antimicrob. Chemother.* **36**, 215-218.

70. Jones, R.B., Van Der Pol, B., Johnson, R.B. (1996). Susceptibility of *Chlamydia trachomatis* to trovafloxacin. *J. Antimicrob. Chemother.* (Suppl.) in press.

71. Visalli, M.A., Jacobs, M.R., Appelbaum, P.C. (1996). Activity of CP-99,219 (trovafloxacin) compared with ciprofloxacin, sparfloxacin, clinafloxacin, lomefloxacin, and cefuroxime against ten penicillin-susceptible and penicillin-resistant pneumococci by time-kill methodology. *J. Antimicrob. Chemother.* **37**, 77-84.

72. Spangler, S.K., Jacobs, M.R., Appelbaum, P.C. (1996). Time-kill study of the activity of trovafloxacin compared to ciprofloxacin, sparfloxacin, metronidazole, cefoxitin, piperacillin, and piperacillin/tazobactam against six anaerobes. *J. Antimicrob. Chemother.* (Suppl.) in press.

73. Zinner, S.H., Gilbert, D., Dudley, M.N. (1995). Effect of CP-99,219-27 alone and with ampicillin-sulbactam (A/S) against enterococci. Abstract 336. 7th European Congress of Clinical Microbiology and Infectious Diseases. Vienna, Austria, March 26-30.

75. Chin, N.-X., Neu, H.C. (1987). Post-antibiotic suppressive effect of ciprofloxacin against Gram-positive and Gram-negative bacteria. *Am. J. Med.* **82** (Suppl. 4A), 58-62.

76. Dubois, J., St.-Pierre, C., Gentile, C. (1996). Post-antibiotic effect and human monocyte activity of trovafloxacin against Legionella spp. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract A92, New Orleans, LA, Sept. 15-18.

77. Gootz, T.D., McGuirk, P.R. (1994). New quinolones in development. *Expert Opinion on Investigational Drugs* **3**, 93-114.

78. Pascual, A., Garcia, I., Ballesta, S., Perea, E.J. (1996). Uptake and intracellular activity of trovafloxacin in human phagocytes and tissue cultured epithelial cells. *Abstract A3, 36th Interscience Conference on Antimicrobial Agents and Chemotherapy*, New Orleans, LA, Sept. 15-18.

79. Girard, A.E., Girard, D., Gootz, T.D., Faiella, J.A., Cimochowski, C.R. (1995). *In vivo* efficacy of trovafloxacin (CP-99,219), a new quinolone with extended activities against Gram-positive pathogens, *Streptococcus pneumoniae* and *Bacteroides fragilis*. *Antimicrobial Agents and Chemotherapy* **39**, 2210-2216.

81. Azoulay-Dupuis, E., Bedos, J.P., Valtée, E., Hardy, D.J., Swanson, R.N., Pocidalo, J.J. (1991). Antipneumonoccal activity of ciprofloxacin, ofloxacin, and temafloxacin in an experimental mouse pneumonia model at various stages of the disease. *J. Infect. Dis.* **163**, 319-324.

82. Azoulay-Dupuis, E., Bedos, J.P., Bauchet, J., Rieux, V., Muffat-Joly, M., Carbon, C. (1996). Efficacy of Trovafloxacin (TFX) against penicillin-susceptible (PS) and resistant (PR) strains of *Streptococcus pneumonia* (Sp) in a mouse pneumonia model. *In Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy* ABSTRACT B43, New Orleans, LA.

83. Nau, R., Schmidt, T., Kaye, K., Froula, J.L., Tauber, M.G. (1995). Quinolone antibiotics in therapy of experimental pneumococcal meningitis in rabbits. *Antimicrobial Agents and Chemotherapy* **39**, 593-597.

84. McCracken, G.H., Jr., Sakata, Y. (1985). Antimicrobial therapy of experimental meningitis caused by *streptococcus pneumoniae* strains with different susceptibilities to penicillin. *Antimicrobial Agents and Chemotherapy* **27**, 141-145.

85. Nau, R., Zysk, G., Fischer, F.R., Schmidt, H., Prange, H.W. (1996). Trovafloxacin modulates inflammation in experimental pneumococcal meningitis. *In Abstracts of the 96th American Society for Microbiology General Meeting, New Orleans, LA.* Abstract A-6, p. 134.

86. Kim, Y.S., Liu, Q.X., Chow, L.L., Chambers, H.F., Tauber, M.G. (1996). Trovafloxacin is effective in experimental endocarditis caused by MRSA. Abstract B68, 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, Sept. 15-18.

87. Onderdonk, A.B. (1996) Efficacy of trovafloxacin (CP-99,219), a new fluoroquinolone, in an animal model for intraabdominal sepsis. *Infect. Dis. in Clin. Prac.* **5**: (3 Suppl.): S117-S119.

88. Cisneros, R.L., Onderdonk, A.B. (1989). Efficacy of a combination of ciprofloxacin and clindamycin for the treatment of experimental intraabdominal sepsis. *Curr. Ther. Res.* **4** (Suppl. 5), 959-965.

89. Thadepalli, H., Reddy, U., Chuah, S.K., Thadepalli, F., Malilay, C., Gollapudi, S. (1996). Effect of new quinolone, CP-99,219-27, in curing intraabdominal abscesses in rats. *Infect. Dis. in Clin. Prac.* **5** (3 Suppl.): S120-S121.

90. Khan, A.A., Slifer, T., Araujo, F.G., Remington, J.S. (1996). Trovafloxacin is active against *Toxoplasma gondii*. *Antimicrob. Agents Chemother.* **40**, 1855-1859.

91. Hooper, D.C., Wolfson, J.S. (1993). Mechanisms of bacterial resistance to quinolones. D.C. Hooper and J.S. Wolfson (eds.) *Quinolone Antimicrobial Agents*, 2nd Ed. Chapter 5, pp. 97-118, American Society for Microbiology, Washington, DC.

92. Barry, A.L., Brown, S.D., Fuchs, P.C. (1996). *In vitro* selection of quinolone-resistant staphylococcal mutants by a single exposure to ciprofloxacin or trovafloxacin. *J. Antimicrob. Chemother.* 38: 324-327.

93. Girard, A.E., Cimochowski, C.R., Finegan, S.M., Gootz, T.D. (1996). Trovafloxacin: efficacy versus *Streptococcus pneumoniae* topoisomerase IV mutants and lack of *in vivo* emergence of resistance. Abstract C116, 36th Interscience Conference on Antimicrobial Agents and Chemotherapy. New Orleans, LA, Sept. 15-18.

94. Tankovic, J., Perichon, B., Duval, J., Courvalin, P. (1996). Contribution of mutations in *gyrA* and *parC* genes to fluoroquinolone resistance obtained *in vivo* and *in vitro* mutants of *Streptococcus pneumoniae. Antimicrob. Agents Chemother.* 40: 2505-2510.

97. Freeman, C., Robinson, A., Cooper, B., Mazens-Sullivan, M., Quintiliani, R., Nightingale, C. (1995). *In vitro* antimicrobial susceptibility of glycopeptide-resistant enterococci. *Diagn. Microbiol. Infect. Dis.* **21**, 47-50.

98. Mulazimoglu, L,. Drenning, S.D., Yu, V.L. (1995). *In vitro* activity of two novel oxazolidinones (U-100592 and U-100766), a new fluoroquinolone (CP-99,219-27) and a streptogramin (Synercid) against *S. aureus* and *S. epidermidis.* In *Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California.* Abstract F210, p. 149. American Society for Microbiology, Washington, DC.

100. Andrews, J.M., Brenwald, N.P., Wise, R., Honeybourne, D. (1996). Concentrations of trovafloxacin in lung tissue. Abstract A4, 36th Interscience Conference on Antimicrobial Agents Chemotherapy, New Orleans, LA, Sept. 15-18.

101. Dubois, J., St.-Pierre, C. (1996). An *in vitro* susceptibility study of trovafloxacin against *Legionella* spp. Abstract E75, 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, Sept. 15-18.

102. Dalvie, D., Khosla, N., Vincent, J. (1995). Metabolism of a new quinolone antibiotic, CP-99,219, in humans. In *Proceedings of the Fourth International Society of Study of Xenobiotics (ISSX) Meeting, Seattle, Washington.* Abstract 126, p. 126. International Society of Study of Xenobiotics.

103. Hopkins, S., Williams, D., Dunne, M., Marinovich, L., Edeline, M., Utt, E., Dutse, A. (1996). A randomized, controlled trial of oral or i.v. trovafloxacin versus ceftriaxone in the treatment of epidemic meningococcal meningitis. 36th International Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, Sept. 15-18.

105. Jenkins, S.G. (1996). *In vitro* synergy between trovafloxacin and ampicillin-sulbactam against bacterial pathogens. Abstract E82 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, Sept. 15-18.

106. Visalli, M.A., Bajaksouzian, S., Jacobs, M.R., Appelbaum, P.C. (1996). Activity of trovafloxacin, alone and in combination with other agents, against gram-negative non-fermentative rods, compared with other quinolone and non-quinolone agents. *Antimicrob. Agents Chemother*. (submitted).

APPEARS THIS WAY
ON ORIGINAL

REVIEW FOR HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

JUL 3 1997

Microbiologist's Review #1 of NDA 20-760
June 30, 1997

A. 1. **APPLICATION NUMBER:** 20-760

APPLICANT: Pfizer Inc.
Central Research Division
Eastern Point Road
Groton, CT 06340

2. **PRODUCT NAMES:** Trovan Injection (alatrofloxacin mesylate injection)

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** A sterile solution of 20.6 ml (in a 20 ml vial), 40.9 ml (in a 40 ml vial), and 61.2 ml (in a 60 ml vial) at 5 mg/ml of alatrofloxacin mesylate. It is administered intravenously.

4. **METHOD(S) OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY:** Trovan is indicated for the treatment of bacterial infections in adults 18 years of age and older, and for the treatment of epidemic meningococcal meningitis in children 3 months to 16 years using a 3 mg/ml daily dose.

B. 1. **DATE OF INITIAL SUBMISSION:** December 27, 1996

2. **AMENDMENT:**

3. **RELATED DOCUMENTS:** NDA 20-759

4. **ASSIGNED FOR REVIEW:** February 13, 1997

5. **DATE OF CONSULT REQUEST:** January 29, 1997

C. REMARKS:

Trovan is a synthetic, broad-spectrum antibacterial agent. Alatrofloxacin (bis-alanyl derivative of trovaflaxacin) is the parenterally-administered

It is to be manufactured by Pfizer in Brooklyn, New York.

Alatrofloxacin mesylate injection

The of the drug product. Alatrofloxacin mesylate injection

to the drug product.

D. CONCLUSIONS:

The submission is recommended for approval with regard to microbiology. However, the validation for the should be submitted as part of the post-approval commitment.

/S/ 6/30/97

Brenda Uratani, Ph.D.
Review Microbiologist

/S/ 7/3/97

cc:

NDA 20-760
HFD-520/ Div. File
HFD-805/ Uratani
HFD-520/CSO/ P. Fogarty
HFD-520/Chemist/ B.V. Shetty
drafted by: Brenda Uratani, 6/30/97
R/D initialed by P. Cooney, 6/30/97