V. CONCLUSIONS

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

Trofloxacin 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 trofloxacin. Peak blood levels following multiple 300 mg intravenous doses of alatrofloxacin range

Trofloxacin 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 trofloxacin from 2 to 32-fold. This appears to have a minor effect on the activity of trofloxacin, however, since efficacy in mouse protection studies paralleled the in vitro potency of trofloxacin against challenge pathogens.

The elimination of trofloxacin 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, trofloxacin appears to lack photocotoxic activity and it does not interfere with the metabolism of theophylline. Coadministration of trofloxacin with food does not markedly affect the extent of absorption. Age or gender differences minimally impact the pharmacokinetic profile of trofloxacin.

Trofloxacin seems more active than ciprofloxacin and ofloxacin and as active as sparflaxin against some Gram-positive organisms, and anaerobes. The published susceptibility studies focused on testing the activity of trofloxacin against S. pneumoniae, evaluating a number of penicillin-susceptible and -resistant isolates. The MIC range of trofloxacin against 1,867 penicillin-susceptible pneumococci from nineteen studies and the median MIC₉₀ was 0.125 µg/mL. This degree of activity was 16, 32, and 4-fold greater than that observed with ciprofloxacin, ofloxacin, and sparflaxin, respectively. Trofloxacin is equally active against pneumococci that were penicillin-resistant.

The MIC₉₀ range for trofloxacin 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 ≥ 64 µg/mL) in pneumococci. Trofloxacin 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 x 10⁻⁶. This low mutation frequency, coupled with the fact that resistance loci are not plasmid encoded, suggests that high-level resistance to trofloxacin may not be widespread in S. pneumoniae.

Trofloxacin is more active than ciprofloxacin against staphylococci. Strains of MSSA have an MIC₉₀ range to trofloxacin, 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 MIC₉₀ values 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 MIC₉₀ 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 MIC₉₀ range for 33 isolates. Neither trovafloxacin nor ciprofloxacin were very active against vancomycin-resistant isolates of *E. faecium*. The MIC₉₀ 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 sparflaxin 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 sparflaxin. Median MIC₉₀ values of trovafloxacin were ≤1 μg/mL against *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *M. morganii*. Ciprofloxacin and sparflaxin had better activity than trovafloxacin against *E. cloacae*. Median MIC₉₀ 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 sparflaxin. 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 sparflaxin against 70 isolates of *N. gonorrhoeae*.

Trovanoxacin was active against 50 gonococci with reduced susceptibility to ciprofloxacin (ciprofloxacin MIC₉₀ = 1.0 μg/mL versus trovafloxacin MIC₉₀ = 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 MIC₉₀ range of trovafloxacin against 1,404 isolates of *B. fragilis*
from twelve studies was At the median MIC₉₀ 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. MIC₉₀ of 0.25 verses cipro/oflox. MIC₉₀ of 0.5 µg/mL), C. difficile (trova. MIC₉₀ of 1.0 verses cipro/oflox. MIC₉₀ of 8.0 µg/mL), Fusobacterium spp. (trova. MIC₉₀ of 1.0 verses cipro. MIC₉₀ of 3 µg/mL), and peptostreptococci (trova. MIC₉₀ of 1.0 verses cipro. MIC₉₀ 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 ≤1.0, 2.0, and ≥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 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

B. Interpretive Criteria Established
The following MIC interpretive criteria should be used for testing non-fastidious aerobic organisms
MIC (µg/mL)  
**≤ 1.0**  
**2.0**  
**≥ 4.0**  
**Interpretation**  
Susceptible (S)  
Intermediate (I)  
Resistant (R)
The following zone diameter interpretive criteria should be used for testing *Streptococcus* spp. including *Streptococcus pneumoniae*:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 19</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>18-16</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤ 15</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>MIC (μg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.125</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>0.25</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 0.5</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 37</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>34-36</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤ 33</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>MIC (μg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2.0</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>4.0</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 8.0</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

**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<sub>90</sub> 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<sub>90</sub> of 2.0 µg/mL is not acceptable. This organism 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<sub>90</sub> 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<sub>90</sub> 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<sub>90</sub> is >8.0 µg/mL. *Acinetobacter baumanii* will not be allowed in the label.

*Alcaligenes faecalis*  
There are few isolates and the MIC<sub>90</sub> 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<sub>90</sub> 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<sub>90</sub> 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<sub>90</sub> 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<sub>90</sub> 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<sub>90</sub> 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<sub>90</sub> 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<sub>90</sub> 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<sub>90</sub>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<sub>90</sub> 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<sub>90</sub> 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<sub>90</sub> 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<sub>90</sub> 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<sub>90</sub> 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 melanogenica*
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 melanogenica* in the label. *Prevotella melanogenica* will not be allowed.

**Other microorganisms:**

*Legionella dumoffii*
Trovafoxacin 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 trovafoxacin 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 trovafoxacin 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 trovafoxacin and the mentioned classes of antibiotics. The overall results obtained from in vitro synergy studies, testing combinations of trovafoxacin 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 trovafoxacin in vitro develops slowly via multiple-step mutation in a manner similar to other fluoroquinolones. Resistance to trovafoxacin in vitro occurs at a general frequency of between Although cross-resistance has been observed between trovafoxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to trovafoxacin.

Trovafoxacin 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** (meticillin-susceptible strains)
- **Staphylococcus epidermidis** (meticillin-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 methods¹ (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

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2.0</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>4.0</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 8.0</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

For testing *Haemophilus* spp.²:

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation³</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.0</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

² These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using Haemophilus Test Medium (HTM)⁴

³ 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*⁵:

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.0</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>2.0</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 4.0</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

⁵ 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*⁶:

APPEARS THIS WAY ON ORIGINAL
MIC (μg/mL) | Interpretation
---|---
≤ 0.125 | Susceptible (S)
0.25 | Intermediate (I)
≥ 0.5 | Resistant (R)

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

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:

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>MIC Range (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em> ATCC 25922</td>
<td>0.004-0.016</td>
</tr>
<tr>
<td><em>S. aureus</em> ATCC 29213</td>
<td>0.008-0.03</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> ATCC 27853</td>
<td>0.25-2.0</td>
</tr>
<tr>
<td><em>E. faecalis</em> ATCC 29212</td>
<td>0.06-0.25</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> ATCC 49247</td>
<td>0.004-0.016</td>
</tr>
<tr>
<td><em>S. pneumoniae</em> ATCC 49619</td>
<td>0.06-0.25</td>
</tr>
<tr>
<td><em>N. gonorrhoeae</em> ATCC 49226</td>
<td>0.004-0.016</td>
</tr>
</tbody>
</table>

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

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

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 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:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 17</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>14-16</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤ 13</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

For testing *Haemophilus* spp.:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 22</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

¹ These zone diameter standards are applicable only to tests with *Haemophilus* spp.

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*:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 19</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>18-16</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤ 15</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

These zone diameter standards only apply to tests performed

For testing *Neisseria gonorrhoeae*:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 37</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>34-36</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤ 33</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

These interpretive standards are applicable to disk diffusion tests with GC agar base and 1% defined growth supplement² incubated in 5% CO₂.

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:

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Zone Diameter Range (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em> ATCC 25922</td>
<td>29-36</td>
</tr>
<tr>
<td><em>S. aureus</em> ATCC 25923</td>
<td>29-35</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> ATCC 27853</td>
<td>21-27</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> ATCC 49247</td>
<td>32-39</td>
</tr>
<tr>
<td><em>S. pneumoniae</em> ATCC 49619</td>
<td>25-32</td>
</tr>
<tr>
<td><em>N. gonorrhoeae</em> ATCC 49226</td>
<td>42-55</td>
</tr>
</tbody>
</table>

¹ This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49247.

² This quality control range is applicable only to tests performed by disk diffusion.

³ 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. The MIC values obtained should be interpreted according to the following criteria:

<table>
<thead>
<tr>
<th>MIC (μg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2.0</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>4.0</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 8.0</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>MIC* (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bacteroides fragilis</em> ATCC 25285</td>
<td>0.125-0.5</td>
</tr>
<tr>
<td><em>Bacteroides thetaotaomicron</em> ATCC 29741</td>
<td>0.25-1.0</td>
</tr>
<tr>
<td><em>Eubacterium lentum</em> ATCC 43055</td>
<td>0.25-1.0</td>
</tr>
</tbody>
</table>

* These quality control ranges were derived from tests performed.

**References:**


/S/

Sousan Sayahtaheri Altaie, Ph.D.
Clinical Microbiology Review Officer

Orig. NDA
HPD-520/Division File
HPD-590/Division File
HPD-590/TL MO B Leissa
HPD-520/TL MO M Makhene
HPD-500/TL MO D Davis
HPD-590/TL MO R Alvisatos
HPD-590/TL MO P Coyne
HPD-590/TL MO R Roca
HPD-520/TL Pharm/A Ellis
HPD-520/TL Chem/BV Shetty
HPD-520/TL Micro/AT Sheldon

Concurrence Only:
HPD-520/DepDir/L Gavrilovich
HPD-590/Dep Dir/R Albrecht
HPD-520/TL Micro/AT Sheldon

APPEARS THIS WAY ON ORIGINAL

/S/ 12/29/97

APPEARS THIS WAY ON ORIGINAL
BIBLIOGRAPHY


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

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

2. **PRODUCT NAMES:** Trovan Injection (alatrofloxac in 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 alatrofloxac in 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. Aatrofloxacin (bis-alanyl derivative of trovafloxacin) is the parenterally-administered product. Aatrofloxacin mesylate injection to the drug product.

D. CONCLUSIONS:

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

/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