

*P. aeruginosa*. The reason for this is unclear but may possibly be due to the low number of patients in the Spanish arm.

For MITT patients with *P. aeruginosa* regardless of country of origin, the rates of clinical failure were lower for patients treated with ciprofloxacin than patients treated with PNH. For MITT patients with *S. aureus* regardless of country of origin, the rates of clinical failure were similar for patients treated with ciprofloxacin than patients treated with PNH.

Similar results to the Pivotal Study were seen in the study by Pistorius et al. [38]. Bacteriologic success (eradication or presumed eradication at EOT) occurred in 92% of patients in the ciprofloxacin group, 95% in the ciprofloxacin plus HD group, and 87% in the PNH group. In study CIFLOT III/00-01, the proportions of patients with eradication or presumed eradication were between 82% and 98%, depending on the population and treatment group, and were slightly greater for Cetraxal Plus than for ciprofloxacin 0.3%. In a published study comparing ciprofloxacin 0.2% and oxytetracycline/polymyxin B/HC [6], a larger proportion of patients had eradication with ciprofloxacin than with the comparator. In several open-label, uncontrolled published studies [2, 4, 5] over 90% of patients experienced eradication of pathogens after otic treatment with ciprofloxacin 0.3%.

The results of these clinical microbiology studies suggest that treatment with Ciprofloxacin Otic Solution 0.2% is effective in eradicating *S. aureus* and *P. aeruginosa* associated OE. The span of time over which ciprofloxacin has demonstrated effectiveness against pathogens commonly associated with OE suggests that localized topical administration of antibiotics may help to avoid the development of resistant *S. aureus* and *P. aeruginosa*. In general, topical ciprofloxacin treatment appeared to be at least as effective as PNH in the treatment of OE.

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## INTRODUCTION

Ciprofloxacin Otic Solution 0.2% is a fluoroquinolone agent with broad-spectrum antibacterial activity. Due to their broad spectrum of antibacterial activity, fluoroquinolones are increasingly of interest in the topical treatment of common ear infections. In addition, fluoroquinolones are rarely associated with contact hypersensitivity and are unlikely to have ototoxic effects. Ciprofloxacin was the first fluoroquinolone available as an ototopical treatment.

Ciprofloxacin is a well-characterized active ingredient that has been used extensively for the treatment of otitis externa (OE). It has been shown to be effective against pathogens commonly identified with OE, including *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus*. Since World War II, the estimates of the incidence rates for which these two microorganisms have been identified as the causative pathogens in cases of OE have varied greatly. However, recent studies report a 45% incidence of *P. aeruginosa* in adults and 54% in children. *S. aureus* was the pathogen identified at pre-therapy in 13% of adults and 10% of children [12-14].

Extensive *in vivo*, *in vitro*, and clinical studies have been conducted with ciprofloxacin to evaluate its antimicrobial activity. In the Core and several of the published studies, the pathogens associated with OE have been identified and, when tested, demonstrated a high level of susceptibility to ciprofloxacin.

**Reviewer's comments:** Otitis externa refers to a variety of infections of the external auditory canal and auricle. It is a common condition and affects 5-- 20% of patients attending ENT clinics [15].

Cerumen (ear wax) is composed of secretions produced by the sebaceous and apocrine glands admixed with desquamated epithelial cells. Its acidic coat creates an inhospitable environment for pathogens and it also produces antimicrobial compounds such as lysozyme. The canal itself is a self-cleansing structure as the cerumen coat migrates laterally and sloughs externally.

Acute diffuse otitis externa is a bacterial infection of the canal caused by a break in the normal skin/cerumen protective barrier in the presence of elevated humidity and temperature. Infection is often introduced by minor abrasions or injuries to the layer or by the presence of water in the ear canal. This infection is often referred to as "swimmer's ear". The infection is characterized by pain, itch, deafness, and fullness. Signs on examination include erythema, edema, purulent otorrhea and crusting of the canal wall skin.

The two most common organisms isolated in the external auditory canal of normal individuals are the *Staphylococcus* species (*S. auricularis*, *S. epidermidis*, *S. capitis*) and the *Corynebacterium* species (*Turicella stitidis*, *C. auris*). The third most frequently recovered bacteria are the *Streptococci* and *Enterococci* group (*Alloiococcus otitis*). Together, they account for more than 90% of the normal flora in the external auditory canal. *Pseudomonas aeruginosa*, *S. epidermidis* and *S. aureus* are the three most common pathogens isolated in acute diffuse otitis externa.

The key to success in managing external ear infection is regular and meticulous aural cleansing. Once the ear is cleaned, an antibiotic/steroid eardrop is administered for one week. Topical antibiotics and steroids are based in an acidic solution to inhibit bacterial growth and many contain glycerol, which acts as a desiccant.

Eardrops containing gentamicin or polymyxin appear to be most effective against the three most common bacteria. Ciprofloxacin/ofloxacin otic solution is a new topical formulation that has a wide spectrum of activity against most common ear pathogens. Even though some organism may

been proposed that DNA gyrase is probably more lethal to the cell than inhibition of topoisomerase IV. Thus, for clinical bacterial isolates the DNA gyrase is often more commonly targeted in resistance mutants.

**Table 1. Range of Inhibitory Concentrations of Ciprofloxacin for DNA Gyrase and Topoisomerase IV for Several Bacterial Species.**

organism	IC50 (µg/ml)	
	DNA gyrase	Topo IV
<i>S. pneumoniae</i>	80-138	5-7
<i>S. aureus</i>	13.5-25	4-6
<i>E. coli</i>	< 0.75	2
<i>P. aeruginosa</i>	0.5	4

Source: Table 1, Section 5.3.5.4.2, p5

### SPECTRUM OF ACTIVITY

In section 2.6.2.2.2, Module 2, Volume 1.1, this submission, the Applicant asserts that *in vitro* antimicrobial effects of ciprofloxacin are well characterized and well documented. *Note: the Applicant provides no recent data to support this assertion. Instead, the Applicant provides the Spectrum of Activity section of the Microbiology Section of the Package Insert from Cipro® HC Otic.*

A summary of review literature and information regarding the prescribing information of ciprofloxacin is provided in this section (Cipro® HC Otic Prescribing Information, Tab 4.3.2, Module 4, Volume 2, this submission; Cipro PI, Tab 4.3.3, Module 4, Volume 2; Mosby Drug Consult [19]).

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical trials.

#### Aerobic Gram-Positive Microorganisms

*Enterococcus faecalis* (many strains are only moderately susceptible), *Staphylococcus aureus* (methicillin-susceptible strains only), *Staphylococcus epidermidis* (methicillin-susceptible strains only), *Staphylococcus saprophyticus*, *Streptococcus pneumoniae* (penicillin-susceptible strains only), *Streptococcus pyogenes*.

#### Aerobic Gram-Negative Microorganisms

*Campylobacter jejuni*, *Citrobacter diversus*, *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Morganella morganii*, *Neisseria gonorrhoeae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia rettgeri*, *Providencia stuartii*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Serratia marcescens*, *Shigella boydii*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*.

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker.

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

exhibit resistance to antibiotics *in vitro*, the high concentration of antibiotics in topical antibiotic preparations is lethal to those resistant organisms, provided the topical solution can penetrate to infected tissues.

## PRECLINICAL EFFICACY—*IN VITRO*

### MECHANISM OF ACTION

Fluoroquinolones (and earlier quinolones) are novel among antimicrobial agents in clinical use because they directly inhibit bacterial deoxyribonucleic acid (DNA) synthesis [16]. Two enzymes, DNA gyrase and topoisomerase IV, are the principal targets for the antibacterial activity of the fluoroquinolones. As bacterial DNA is a double-stranded, circular and coiled molecule, efficient DNA replication requires systematic unwinding and preservation. Replication proceeds in a stepwise manner along the DNA circle, progressing along a continuously advancing point termed the replication fork. As the replication fork advances, helical stress is introduced, thereby creating unwanted supercoils. If unresolved, the stress renders the cell incapable of DNA replication.

The two enzymes, DNA gyrase and topoisomerase IV, are structurally related to each other as both are tetrameric with pairs of two different subunits. These subunits serve to reduce this stress by restoring the proper conformation structure of the bacterial DNA [16, 17]. The GyrA and GyrB subunits of DNA gyrase are respectively homologous with the ParC and ParE subunits of topoisomerase IV. Both enzymes are type 2 topoisomerases, which act by breaking both strands of a segment of DNA, passing another segment through the break, and then resealing the break. For DNA gyrase, this topoisomerization reaction results in introduction (or removal) of DNA supercoils, thus affecting the negative supercoiling of DNA necessary to initiate replication and remove positive supercoils that accumulate before an advancing replication fork. For topoisomerase IV, the topoisomerization reaction results in separation of the interlocking of daughter DNA strands that develop during replication; this facilitates the segregation of daughter DNA molecules into daughter cells. In both cases, fluoroquinolones appear to trap the enzyme on DNA during the topoisomerization reaction, forming a physical barrier to the movement of the replication fork, RNA polymerase, and DNA helicase. The eventual molecular interaction of the replication fork, with these trapped complexes triggers other poorly defined events within the cell that ultimately result in cell death (possibly from the release of DNA ends that may be involved in the induction of apoptosis).

Both topoisomerase enzymes are essential for bacterial growth, but they cannot complement one another [18]. Several studies have highlighted substantial variations in the *in vitro* inhibitory concentrations for DNA gyrase and topoisomerase IV, depending on both the bacterial species and the particular quinolone molecule being studied (see Table I below). These data, which are roughly consistent with MIC values and data obtained from analysis of resistant mutants, confirm that DNA gyrase is the preferred target of fluoroquinolones in Gram-negative bacteria. For Gram-positive bacteria, it is not as straightforward in that whereas topoisomerase IV may be the preferred target, it has

Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 µg/ml or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

**Aerobic Gram-Positive Microorganisms**

*Staphylococcus haemolyticus*, *Staphylococcus hominis*, *Streptococcus pneumoniae* (penicillin-resistant strains only).

**Aerobic Gram-Negative Microorganisms**

*Acinetobacter lwoffii*, *Aeromonas hydrophila*, *Edwardsiella tarda*, *Enterobacter aerogenes*, *Klebsiella oxytoca*, *Legionella pneumophila*, *Pasteurella multocida*, *Salmonella enteritidis*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Vibrio vulnificus*, *Yersinia enterocolitica*.

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

Susceptibility of Gram-negative pathogens to several antibiotics has also been evaluated extensively via the SENTRY Antimicrobial Surveillance Program from 1997-2001 where a total of 48,440 *Enterobacteriaceae* isolates were collected consecutively from patients hospitalized in participating hospitals in four regions: Asia-Pacific, Europe, Latin America, and North America [20]. These isolates were tested by reference broth microdilution method against the most commonly used antimicrobial agents, including ciprofloxacin. Of the pathogens isolated, *E. coli* was the most frequently isolated (46.1%), followed by *Klebsiella* spp. (21.3%), and *Enterobacter* spp. (12.2%). Of the three classes of antimicrobial agents tested, the fluoroquinolones demonstrated good susceptibility similar to the β-lactams. Table 2 indicates the activity of ciprofloxacin tested against the 48,440 *Enterobacteriaceae* isolates:

**Table 2. Susceptibility of Gram-Negatives to Ciprofloxacin: SENTRY 48,440 Isolates.**

Cumulative % inhibited at MIC (µg/ml) of:					
0.25	0.5	1	2	%S*	%R*
86.9	88.9	90.5	91.7	90.5	8.3

\*Susceptibility (S) and resistance (R) interpretive criteria of the CLSI (2003)  
Source: Table 2.1, section 5.3.5.4.3, p8

The SENTRY Program also evaluated the occurrence and antimicrobial susceptibility patterns of non-fermentative Gram-negative bacilli (NFB) during 1997-2001 via the evaluation of 18,569 NFB isolates from the four indicated regions [21]. Of these, *P. aeruginosa* was the most frequently isolated pathogen (64.5%), followed by *Acinetobacter* spp. (18.7%) and *S. maltophilia* (8.0%). Table 3 indicates the activity of

ciprofloxacin tested against the 11,968 strains of *P. aeruginosa* isolated in the SENTRY program worldwide:

**Table 3. Susceptibility of NFB to Ciprofloxacin: SENTRY (18,569 isolates).**

Cumulative % inhibited at MIC ( $\mu\text{g/ml}$ ) of:					
0.25	0.5	1	2	%S	%R*
58	67	73	78	73	22

\*Susceptibility (S) and resistance (R) interpretive criteria of the CLSI (2003)  
 Source: Table 2.2, section 5.3.5.4.3, p8

Similar to the SENTRY database used to evaluate the *Enterobacteriaceae* and NFB organisms, a study was performed to determine the susceptibility among commonly isolated Gram-negative bacilli to fluoroquinolones during January 1 and May 31, 2000 using the TRUST and TSN databases (TRUST= Tracking Resistance in the United States Today; TSN = The Surveillance Network) [22]. The TRUST surveillance database originally involved 27 hospital microbiology laboratories in the US forwarding clinical isolates to a central laboratory for susceptibility testing. In this particular study 26 hospital laboratories from the US participated of which 23 were in the original TRUST surveillance group. The TSN, established in 1994, is a database that electronically assimilates daily antimicrobial susceptibility testing and patient demographic data from the US, France, Germany, Italy, and Spain. As fluoroquinolones have been used extensively as broad-spectrum agents for infections, especially those caused by Gram-negative bacilli for the past two decades, this study was important to determine the susceptibility and monitor any increase in resistance. A total of 2,519 *Enterobacteriaceae* and 580 NFB isolates from TRUST were evaluated with a much larger number evaluated from the electronic TSN database. Table 4 depicts the *in vitro* activity of ciprofloxacin against *E. coli*, *P. mirabilis*, and *P. aeruginosa*.

**Table 4. Susceptibility of Enterobacteriaceae and NFB to Ciprofloxacin: TRUST and TSN (total of 2,519 and 580).**

Species	TRUST		TSN	
	N	S (%)	N	S (%)
<i>E. coli</i>	655	94.5	76,600	96
<i>P. mirabilis</i>	430	87.7	9793	87.4
<i>P. aeruginosa</i>	404	73.5	25,073	66.4

Source: Table 2.3, section 5.3.5.4.3, p8

Susceptibility for all organisms associated with a range of skin and soft tissue infections (SSTI) in hospitalized patients were studied using data contained within TSN (as noted above) [23]. The data reported to TSN by participating clinical laboratories and used for the SSTI evaluation were obtained during 2001. This analysis determined the incidence of species and their susceptibility to antimicrobial agents commonly tested in clinical laboratories throughout the participating regions, including the use of ciprofloxacin. During the year studied (2001), *S. aureus*, *Enterococcus* spp., *E. coli*, and *P. aeruginosa* were the most common organisms isolated and susceptibility tested (including 20,248 strains in the U.S. from 283 sites; 8,148 strains in Spain from 21 sites). Table 5 represents

the activity of ciprofloxacin against Gram-positive organisms isolated from SSTI inpatients.

**Table 5. Susceptibility of MSSA and MRSA to Ciprofloxacin in the US and Spain: TSN (20,248).**

Country	Strain	Total N	%S <sup>a</sup>	% <sup>b</sup>	%R <sup>c</sup>
United States	MSSA <sup>d</sup>	1924	91.4	2.4	6.2
	MRSA <sup>e</sup>	1510	14.9	1.2	83.9
Spain	MSSA <sup>d</sup>	1324	93.3	1.4	5.4
	MRSA <sup>e</sup>	642	4.2	0.5	95.3

a=susceptible, b=intermediate, c=resistant, d=mediclin-susceptible *S. aureus*, e=mediclin-resistant *S. aureus* [44.4% were MRSA in the US with 32.45 in Spain]

Source: Table 2.4, section 5.3.5.4.3, p9

Another study to evaluate the occurrence and antimicrobial susceptibility patterns of SSTI was performed using the SENTRY database for North America (U.S. and Canada) for isolates collected during October and December 2000 [24]. In this study, a total of 1,404 isolates were recovered from SSTI from 24 hospital sites in the US and five in Canada. Of those collected, the most frequently isolated were *S. aureus* (45.9%), *P. aeruginosa* (10.8%), *Enterococcus* spp. (8.2%), *E. coli* (7.0%), *Enterobacter* spp. (5.8%), and *Klebsiella* spp. (5.1%). The same order was observed in both the U.S. and Canada. Of the isolates, almost 30% of *S. aureus* were oxacillin-resistant. The following table represents the *in vitro* activity of ciprofloxacin against the five most frequent pathogens causing SSTIs.

**Table 6. Susceptibility of SSTI Organisms to Ciprofloxacin SENTRY (North America), 1404 isolates.**

Species	N	MIC <sub>50</sub>	MIC <sub>90</sub>	%R
<i>S. aureus</i>	777	≤ 0.25	> 2	28.5
<i>P. aeruginosa</i>	152	< 0.25	> 2	20.4
<i>E. coli</i>	98	≤ 0.25	> 2	12.2
<i>Enterobacter</i> spp.	81	≤ 0.25	0.5	2.5
<i>Klebsiella</i> spp.	71	≤ 0.25	2	9.9

Source: Table 2.8, section 5.3.5.4.3, p10

These results demonstrate that the *in vitro* antimicrobial efficacy of ciprofloxacin against pathogens is well established and documented. However, it should be noted that the microbiological epidemiologic databases noted above, SENTRY and TSN, obtain their clinical bacterial pathogens primarily from hospital microbiology labs and thus likely include a significant proportion of patients with hospital-acquired infections, thereby increasing the number of bacteria with antimicrobial resistance. The Applicant believes that this then probably represents a worse-case scenario for determining *in vitro* activity of ciprofloxacin against pathogens isolated from a primarily community-acquired infection such as otitis externa and can be contrasted against the susceptibility testing results from the clinical trial that is the subject of this NDA submission (Section 5.3.5.4.11, this submission) and that of data from previously published studies (Section 5.3.5.4.18, this submission) which demonstrate high percentages of organisms susceptible to ciprofloxacin.