

**Reviewer's comments:** The Applicant presents a list of organisms from the package insert for Ciprofloxacin HC that show susceptibility to ciprofloxacin. However, there are no specific data presented here. That is, there are *no data* for *MIC<sub>50s</sub>*, *MIC<sub>90s</sub>*, *MIC range*, *disk zone sizes*, etc. MIC interpretations are based on the interpretive criteria established for the systemic use of ciprofloxacin. These criteria are of limited use as the use of topical antibiotics is not based upon susceptibility breakpoints since the concentration of ciprofloxacin applied in this indication is several times the concentration achievable in the serum. The referenced package insert is from a NDA filed in 1987 for Cipro® HC thus the referenced data are not recent. The surveillance data from SENTRY, TRUST and TSN are within the past five years and thus, the data are more recent. However, MIC ranges are not presented. Microbiology defines "recent" susceptibility data as data generated *within the past three years*. However, it should be noted that recent data in the published literature on the susceptibility of *S. aureus* and *P. aeruginosa* to ciprofloxacin is not abundant.

### **MECHANISMS OF RESISTANCE**

Bacterial resistance to quinolones can develop through chromosomally- or plasmid-mediated mechanisms. Chromosomal mutations, currently the most commonly reported mechanism for quinolone resistance, can alter the targets, DNA gyrase and topoisomerase IV, or it can also occur through a decrease in the intrabacterial concentration of a drug [25].

Target site alteration is a result of mutations in the chromosomal genes encoding the DNA gyrase and topoisomerase IV. The mutations most likely occur due to transcription errors during chromosome replication. The target alterations most commonly occur to the *gyrA* and *parC* genes in a region called the 'quinolone resistance-determining region' and result in reduced drug affinity. The effect of the mutations on resistance in the target sites varies with the bacterial species, the gene involved and the quinolone used [25]. Firststep mutations are sufficient to cause clinically important levels of resistance in *P. aeruginosa* and *S. aureus*. Highly resistant clinical isolates, e.g. *E. coli*, *Salmonella* sp., often require multiple mutations to induce clinically important resistance [25, 26].

The other chromosomal mechanism leading to bacterial resistance is the decrease in the intrabacterial concentration of the quinolone. Decreased uptake of the quinolone is a result of changes in the outer membrane, including outer-membrane porin reduction that leads to decreased entry of antibiotics. This usually occurs in combination with other resistant mechanisms such as increased efflux. Efflux is increasingly implicated as a major mechanism of resistance. Efflux pumps can either work with other resistance mechanisms, e.g., mutations in the target enzymes, or express themselves inherently by intrinsic resistance. Efflux encourages resistant mutations by enabling bacteria to survive in sub-optimal concentrations of antibiotics [25, 26].

Plasmid-mediated resistance works through the gene, *qnr*. The *qnr* gene encodes the protein Qnr which protects DNA gyrase and confers resistance to a number of antibiotics, including ciprofloxacin, through increased spontaneous mutations [27].

Resistance to ciprofloxacin as well as other antibiotics is being tracked by the Antimicrobial Resistance Management (ARM) Program developed and run by the

University of Florida [28]. ARM is an ongoing project designed to document trends in antimicrobial susceptibility patterns in inpatient and outpatient isolates and to identify relationships between antibiotic use and resistance rates. The participants include qualifying US hospitals that participate in the program, and the data become part of a national aggregate database to provide benchmarks. As of April 11, 2005, 278 (79%) non-teaching and 74 (21%) teaching hospitals have participated in ARM. Each hospital provides a minimum of three years of sensitivity report data while individual antibiotics and organisms are captured in the database.

The Applicant provides charts that depict the national susceptibility/resistance trends for *P. aeruginosa*, *S. aureus*, and *E. coli* and *P. mirabilis* to represent Gram-negative enteric rods (see section 5.3.5.4.4, pp 12-13, in this submission). These interpretations are based on the interpretive criteria established for the systemic use of ciprofloxacin.

The following table depicts the percentage of ciprofloxacin resistance calculated nationally for each organism shown.

**Table 7. Percentage of Ciprofloxacin Susceptible Organisms (US).**

	1998	1999	2000	2001	2002	2003	2004
<i>P. aeruginosa</i>	71.90%	66.10%	63.90%	61.70%	62.20%	61.10%	65.30%
	n=36,629	n=36,853	n=43,149	n=37,699	n=29,894	n=19,560	n=4293
<i>S. aureus</i>	64%	55.80%	55.50%	56.10%	57.10%	53.30%	50.70%
	n=48,269	n=54,628	n=55,470	n=47,590	n=36,509	n=21,551	n=5941
<i>E. coli</i>	97.70%	95.70%	93.40%	93.10%	90.40%	86.50%	84.30%
	n=88,236	n=91,973	n=102,994	n=116,491	93,437	49,529	n=9211
<i>P. mirabilis</i>	86.70%	82.70%	76.70%	74.80%	68.90%	66%	66.90%
	n=15,293	n=17,879	n=20,406	n=19,299	n=16,129	n=9152	n=1662

Source: Un-numbered table, section 5.3.5.4.4, p14

Of concern is the declining sensitivity of the representative bacterial pathogens, shown above, to ciprofloxacin. The overuse, and misuse, of quinolones has led to some of this resistance. To limit the increased resistance to antimicrobials, such as fluoroquinolones, requires the close surveillance of susceptibilities at the local level, the development of policies that restrict unnecessary use, better use of pharmacodynamic and pharmacokinetic data of antibiotics and more systematic collection of MIC measurements to enable more accurate dosing of patients [25, 26].

As discussed earlier, these large microbiological epidemiologic surveillance networks collect bacterial pathogens primarily from hospital based microbiology laboratories and thus these bacterial strain collections contain significant percentages of hospital-acquired bacteria. However, some of these bacteria can make their way into the surrounding communities. Thus, one of the potential advantages of topical therapy is the prevention of resistance generation by exposing the possible pathogens to high local concentrations of active antibiotics. Additionally, the use of topical antibiotics limits the exposure of bacterial flora outside the target area to the active antibiotic and may help reduce bacterial resistance from being created in non-target bacteria. Further discussion of

bacterial resistance in the clinical setting is located in Section 5.3.5.4.11, Sensitivity of Pathogens to Antibiotics, this submission.

**Reviewer's comments:** A recent search of the FOCUS database by this Reviewer (16 March 2006) yielded data indicating reduced susceptibility to ciprofloxacin by both *S. aureus* and *P. aeruginosa*. Susceptibility to ciprofloxacin in *S. aureus* decreased from 58.8% of total isolates (N=63,664) in 2005 to 57.3% of total isolates (N=5050) in 2006. Susceptibility to ciprofloxacin in *P. aeruginosa* decreased from 66.2% of total isolates (N=68,511) in 2005 to 64.1% of total isolates (N=5350) in 2006. Resistance to ciprofloxacin in *S. aureus* increased from 37.7% of total isolates (N=23,923) in 2005 to 38.3% of total isolates (N=2894) in 2006. Resistance to ciprofloxacin in *P. aeruginosa* increased from 28.1% of total isolates (N=19,281) in 2005 to 29.4% of total isolates (N=1573) in 2006. The changes in susceptibility and resistance to ciprofloxacin in both organisms were not dramatic when the data from 2005 are compared to 2006.

However, when the 2005 and 2006 data are compared to the data provided in the ARM data for organisms isolated in SSTIs, ciprofloxacin resistance in *S. aureus* and *P. aeruginosa* has increased. Resistance to ciprofloxacin in *S. aureus* increased from 26.5% of total isolates in 2000 (SENTRY data) to 38.3% of total isolates (FOCUS data) in 2006. Resistance to ciprofloxacin in *P. aeruginosa* increased from 20.4% of total isolates in 2000 (SENTRY data) to 29.4% of total isolates in 2006 (FOCUS data). While the resistance data from the SSTIs may be high due to the prevalence of nosocomial infections which tend to display more antibiotic resistance than community-acquired infections, the increase in resistance is disconcerting, nonetheless.

#### **EPIDEMIOLOGIC STUDIES**

Hwang et al. report that *S. aureus* has become more common than *P. aeruginosa* in acute otitis externa in Taiwan since 1986 [29]. The incidence of MRSA had increased from 2% in 1974 to ~50% in 1997. The resistance of MRSA to ciprofloxacin has also been reported by several investigators.

Gilbert et al. studied the *in vitro* development of phenotypic resistance to fluoroquinolones in single exposure and serial passage experiments with *S. aureus* and *P. aeruginosa* [30]. Based on the single passage experiments, MSSA and MRSA phenotypic resistance to ciprofloxacin develops rapidly. These investigators observed an increase in MIC<sub>90</sub> from 0.5 µg/ml at pre-serial passage for both MSSA and MRSA to post-serial passage MIC<sub>90</sub> of 64 and 128 µg/ml for MSSA and MRSA, respectively. The goal of these experiments was to study changes in the MIC over time under the influence of repeated drug exposure, as might happen clinically to the endogenous flora of the skin, nasopharynx or gastrointestinal tract. The results indicate the potential for creating fluoroquinolone resistance in the organisms and drugs tested.

Viray et al. reported that 60% of all *P. aeruginosa* isolates from three long-term care facilities were susceptible to ciprofloxacin [31]. This value is considerable less than those from isolates from previous years. Taken with the data presented from the Applicant, this would indicate that the susceptibility of *P. aeruginosa* to ciprofloxacin has decreased over time.

## **PRECLINICAL EFFICACY—*IN VIVO***

#### **PHARMACOKINETICS AND PHARMACODYNAMICS**

Generally quinolones show excellent bioavailability as they are characterized by excellent penetration into most tissues and body fluids although the serum levels are unusually low, especially when fractionated dosing schedules are used [18]. Early studies showed that quinolones, like aminoglycosides but in contrast to β-lactams, work mainly in a concentration-dependent manner and exert a marked post-antibiotic effect, although

not consistent across all species. At lower values, the AUC24h/MIC ratio became more predictive, perhaps because of the decreased rate of bacterial killing.

Due to declining rates of failure and emergence of resistance to ciprofloxacin when treating infections caused by organisms with an MIC close to the breakpoints with the commonly used low dosage (2 X 200 mg), a large-scale clinical study was performed that aimed to define the PD parameters that were predictors of efficacy. Univariate analysis showed that the AUC24h/MIC ratio (>125) linked best with both the clinical and microbiological outcomes, and that a C<sub>max</sub>/MIC ratio of < 4 was associated significantly with a sub-optimal outcome. However, the use of twice and three-times daily dosing schedules did not allow analysis of the benefits of high peak concentrations since these were infrequent. After a second experiment stressed the importance of the C<sub>max</sub>/MIC ratio, most investigators and drug companies adopted the AUC24h/MIC ratio as a practical predictive parameter for efficacy as this parameter appeared to be linked strongly to clinical outcome and was largely independent of the dosing interval, the fluoroquinolone used, the animal species and the site of infection.

Evaluating both experimental studies and clinical data, levels of drug exposure depend critically upon the desired effect. Moving from an EC<sub>50</sub> to an EC<sub>99</sub> effect with *in vitro* dynamic models requires an increase of about 10-fold in AUC/MIC ratios. Clinical data also point to the same conclusion by showing that an AUC24h/MIC ratio of 125 will yield efficacy by day seven, but that higher values (>250) will produce faster bacterial eradication. Therefore, time-related events must also be taken into consideration. This may imply that aiming at minimal values may be dangerous, however the C<sub>max</sub>/MIC ratio may be critical in preventing the emergence of resistance and quinolones with a higher C<sub>max</sub> are probably desirable in this context. Table 8 outlines conservative AUC24h/MIC-based limits of sensitivities for ciprofloxacin (free drug concentration as fluoroquinolones do not participate directly in activity):

**Table 8. Pharmacokinetic parameters for ciprofloxacin used for proposing PK/PD based limits of sensitivity and conditions (6).**

Typical daily dosage	Typical PK values		Proposed PK/PD upper limit		Breakpoints (mg/L)	
	C <sub>max</sub> in mg/L total/free (dose)	AUC24h (mg/hL) total/free	Efficacy	prevention of resistance	EUCAST	CLSI
1000 mg	2.5/1.75 (500 mg PO)	24/18	—————		< 0.5 to > 1 ( < 0.125 to > 2)	< 2-2 > 4

Source: Table 3, section 5.3.5.4.5, p15

b(4)

It should be noted that these parameters apply to systemic levels of ciprofloxacin when administered by the intravenous or oral routes. Extrapolating these PK/PD data to a topically administered agent such as Ciprofloxacin Otic Solution 0.2% poses challenges, but it is likely that the C<sub>max</sub>/MIC parameter plays an important role given the high concentrations of drug that bacteria are exposed to in the external auditory canal. However, because the amount of time a topically administered solution remains in the

external auditory canal may vary considerably, AUC/MIC and length of time above MIC may play less predictable roles. In any event, as noted from the results of the clinical study under review for this NDA and that of previously published studies, favorable PK/PD parameters are present given the high bacteriologic eradication rates for the common pathogens associated with OE.

#### **Pharmacokinetics**

As stated in Section 2.4.3 of this submission, the pharmacokinetics, adsorption, distribution, metabolism, and excretion of ciprofloxacin after systemic administration are well known and summarized in the literature [32]. While the pharmacokinetics for topical ciprofloxacin is more relevant to the current submission, the systemic levels of drug obtained after otological administration are too low for analysis.

A pharmacokinetic study in dogs assessed the level of absorption of ciprofloxacin into the systemic circulation [SALVAT dog PK report, section 2.6.5.4, this submission]. This study demonstrated the levels of absorption of ciprofloxacin after otic application is negligible despite using a higher dose than that of the clinical dose. Assay sensitivity was one of the factors that may have affected the outcome of this study. Ciprofloxacin levels in plasma were determined by high pressure liquid chromatography (HPLC) with UV detection which had a limit of detection of ~~---~~  $\mu\text{g/ml}$  [Table 2.6.5.2, SALVAT Analytical Method]. This study used Cetraxal Otico® as the test article and this product has a different formulation than Ciprofloxacin Otic Solution 0.2%. The excipient differences were summarized earlier in Section 2.4.1.1 and are not expected to decrease the level of ciprofloxacin absorbed. The study used a higher concentration of ciprofloxacin than the drug product, which increased the likelihood of detection in the plasma.

b(4)

This low systemic exposure is also supported by a guinea pig study where very little of the ciprofloxacin passed through the tympanic membrane despite direct application to the tympanic membrane itself [Table 2.6.5.3, 33]. The test article was formulated in 0.9% saline, which is different from that of Ciprofloxacin Otic Solution 0.2%.

No otic specific tissue distribution studies were conducted. Absorbed ciprofloxacin, however, is expected to follow the same distribution pattern after a single oral dose of ciprofloxacin.

Following a single oral dose, ciprofloxacin related radioactivity distributed rapidly into the tissue compartments. Comparatively high levels were found in the kidney, liver, skeletal muscle, pancreas, testes, and cartilage relative to plasma. Low drug related equivalents occurred in the brain, eye, and adipose tissue. A similar pattern of distribution was seen after intravenous administration. Highest concentrations were observed at one hour post dose [Table 2.5.5.5., this submission]. It is presumed that after topical treatment, a similar pattern of tissue distribution would be seen.

No metabolism and interspecies comparison studies were conducted. Ciprofloxacin is partially metabolized in the liver by modification of piperazine group to four identified

metabolites which include des-ethylene-ciprofloxacin, sulfo-ciprofloxacin, oxo-ciprofloxacin, and N-formyl-ciprofloxacin. [34].

The plasma elimination half-life ( $t_{1/2\beta}$ ) of ciprofloxacin ranged from 26 to 44 h in rats and monkeys administered ciprofloxacin intravenously or orally. After intravenous administration approximately 51% (rat) and 61% (monkey) was excreted via the kidney. After oral dosing, percent renal excretion was 6-14% (rat) and 30% (monkey). Radioactivity in the urine and feces of rats was predominantly the unchanged drug with one detected but unidentified conjugate. In the monkey, urine, and feces was also predominantly unchanged drug with two detectable metabolites (oxo- and des-ethylene-ciprofloxacin) [Table 2.6.5.5, this submission]. Data for other routes of administration with higher bioavailability and doses may not be applicable to the clinical route of administration given the low absorption observed after otic administration.

Ciprofloxacin clearance is affected by both age and renal impairment. Since the total systemic exposure after dosing Ciprofloxacin Otic Solution 0.2% is very low, these factors are not expected to significantly alter clearance of the otic-absorbed drug.

Three main drug-drug interactions have been described for ciprofloxacin and the class of fluoroquinolones—1) substances that decrease gastrointestinal absorption of ciprofloxacin, 2) alteration of other drug metabolism due to inhibition of specific cytochrome P450 isozymes (CYP1A2 and CYP3A4), and 3) serum protein binding. These specific interactions are well documented from the Agency's findings as summarized in ciprofloxacin product labeling (Approved prescribing information for Cipro®, Module 4, Section 4.3.3, this submission). The drugs cited include theophylline, caffeine, phenytoin, sulfonyleurea, warfarin, probenecid, methotrexate, and non-steroidal anti-inflammatory drugs excluding acetylsalicylic acid.

The Applicant discusses the pharmacokinetics of ciprofloxacin after otic application in Section 2.5.3.1 of this submission.

The Applicant asserts that because of the extent of pharmacology data already available, the Applicant did not conduct clinical pharmacology studies of Ciprofloxacin Otic Solution 0.2% to support this application. The pharmacokinetics and pharmacodynamics of oral and intravenous ciprofloxacin are well characterized [33], but are of limited relevance to an otological formulation instilled into the ear canal of a patient with OE, especially with an intact tympanic membrane. In six Published Studies in children and adults with ear disorders (including patients with intact and non-intact tympanic membranes), ciprofloxacin solution, at concentrations of 0.2%, 0.3%, or 0.5%, was applied in the ear canal, and blood samples were taken to determine serum concentrations of ciprofloxacin. These studies, as summarized in Module 2.7.2.2 of this application, consistently demonstrated that the level of systemic ciprofloxacin after otic application was below the limit of detection. One pharmacokinetic study conducted for NDA 21-537, Ciprodox® Sterile Otic Suspension [36], showed that in children treated with otic ciprofloxacin after tympanostomy tube placement, the systemic absorption of ciprofloxacin was negligible compared to that achieved with oral or intravenous