

# Comparison In Vitro Activity of Garenoxacin Against 618 Clinical Aerobes and Anaerobes Isolated from Clinical Gynecological Infections



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## Revised Abstract

**Background:** Garenoxacin is a novel des-fluoro (6) quinolone which has shown high activity against many aerobes and anaerobes. Evidence of dual targeting of both DNA gyrase and topoisomerase IV gives this compound enhanced activity against gram-positive organisms while retaining significant gram-negative activity. Organisms were isolated from pelvic and gynecological infections as part of a multi-national phase III clinical study. **Methods:** Each isolate was identified using selective growth media and various biochemical profiles. The activity of garenoxacin was compared to 10 relevant antimicrobial agents: amoxicillin/clavulanic acid; ampicillin; ampicillin/sulbactam; aztreonam; ceftriaxone; ciprofloxacin; imipenem; piperacillin/tazobactam; clindamycin; metronidazole. Anaerobic susceptibility testing was performed using Etest methodology (AB Biodisk, Solna, Sweden) following the manufacturer's and NCCLS guidelines. All other organisms were tested using broth microdilution methodology with panels produced by Microscan® (Dade Behring Inc. Sacramento, CA. USA.). Garenoxacin interpretive criteria are based on  $\leq 4$  mcg/mL, susceptible; 8 mcg/mL intermediate;  $\geq 16$  mcg/mL resistant. **Results:** Garenoxacin was the most potent in vitro agent evaluated with 98.8% of all isolates inhibited at a tentative breakpoint of 4 mcg/mL (MIC<sub>50</sub> 0.12 mcg/mL; MIC<sub>90</sub> 0.5 mcg/mL). Garenoxacin activity was comparable to ciprofloxacin (MIC<sub>50</sub> 1 mcg/mL), imipenem (MIC<sub>50</sub> 1 mcg/ml) and piperacillin-tazobactam (MIC<sub>50</sub> 2 mcg/mL), and more active than amoxicillin-clavulanic acid (MIC<sub>50</sub> 8 mcg/mL), ampicillin-sulbactam (MIC<sub>50</sub> 16) and ceftriaxone (MIC<sub>50</sub> 64 mcg/ml) against all study strains. Garenoxacin (MIC<sub>50</sub> 1 mcg/mL) was comparable to all the beta-lactam/beta-lactamase inhibitor compounds (MIC<sub>50</sub> 2 mcg/mL) and more active than clindamycin (MIC<sub>50</sub> 8 mcg/mL) and metronidazole (MIC<sub>50</sub> 64 mcg/mL) against all gram-positive and -negative anaerobes. **Conclusion:** Garenoxacin shows excellent aerobic and anaerobic activity for pathogens common to complicated pelvic and gynecological infections.

## Introduction

Gynecological infections and those of pelvic origin in general are often of mixed variety and can include aerobic and/or anaerobic pathogens. Garenoxacin is an extended spectrum quinolone with enhanced activity against Gram-positive aerobes and anaerobes while retaining significant activity against Gram-negative organisms [1-4]. Using the antimicrobial agent with the most favorable pharmacodynamic activity has been shown to preserve the activity of that drug class and offers the least opportunity for resistance and best outcome for the patient [5]. This in vitro study was undertaken to demonstrate that the activity of one such novel quinolone may be beneficial as a first line agent in the treatment of uncomplicated and complicated infections of gynecological origins.

## Materials and Methods

» Clinical isolates were collected in 2001-2002 from over 300 laboratories.

» 618 isolates of aerobes and anaerobes consisting of 87 species were collected.

» Isolates were identified to genus and species at each site and confirmed by the central laboratory using the RapID ANA II System (Remel Inc. Lenexa, KS) and additional PRAS biochemicals (Anaerobe Systems, Morgan Hill, CA.) as needed.

» Organism collection, transport, confirmation of organism identification, antimicrobial susceptibility testing, as well as, construction and management of a centralized database was coordinated by Laboratories International for Microbiology Studies (LIMS).

## Antimicrobial Susceptibility Testing

» Antibiotics tested were garenoxacin, aztreonam, amoxicillin-clavulanic acid, ampicillin-sulbactam, ceftriaxone, ciprofloxacin, clindamycin, imipenem, metronidazole and piperacillin-tazobactam.

» Aerobic MIC's were determined by the central laboratory using microdilution panels by Microscan® (Dade Behring Inc. Sacramento, CA. USA) according to NCCLS guidelines and manufacturers instructions [6-8].

» Anaerobic MIC's were determined by using the concentration gradient agar diffusion method (Etest, AB Biodisk, Sweden) according to the manufacturers instructions [9].

» Organism suspension was inoculated into Brain Heart Infusion broth equivalent to a 1 McFarland standard.

» Each inoculum was prepared and standardized by using a Microscan turbidity meter to deliver approximately 10<sup>5</sup> CFU/ml. All antibiotic plates were prepared and tested on the same day.

» The determination of endpoints was determined according to NCCLS guidelines [10]. Tentative breakpoints (in terms of mcg/mL) for garenoxacin were defined as susceptible  $\leq 4$ , intermediate 8 and resistant  $\geq 16$ ; for *Staphylococcus* spp that are oxacillin or ciprofloxacin resistant, susceptible  $\leq 2$ , intermediate 4 and resistant  $\geq 8$ .

» PRAS Brucella agar w/Vitamin K and Hemin (Anaerobe Systems, CA) was used as growth medium for testing anaerobes.

» Quality Control of antimicrobial agents, microdilution panels, Etest strips and media was performed using the following ATCC strains: *E. coli* ATCC 35218, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *E. faecalis* ATCC 29212, and *S. aureus* ATCC 29213. *Bacteroides fragilis* ATCC 25285, *Bacteroides thetaiotamicrons* ATCC 29741, *Eubacterium lentum* ATCC 43055.

## Results

The results are presented in the following tables.

Table 1. Aerobic Study Organisms isolated from 456 Clinical Isolates and Anaerobic Study Organisms isolated from 162 Clinical Isolates of Pelvic and Gynecological Origins.

Organism Type	n
Gram-Positive Aerobes	293
Gram Negatives Aerobes	163
Total	456
Gram Positive Anaerobes	80
Gram Negative Anaerobes	82
Total	162
Grand Total	618

Table 2. In Vitro Activity of Garenoxacin and Comparators against all 618 Clinical Pathogens from Pelvic and Gynecological Infections

Antimicrobial	MIC (mcg/mL)			Percent (%)	
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	%Sus	%Res
Garenoxacin	0.094	0.5	$\leq 0.004$ - $>32$	98.9	0.3
Ciprofloxacin	0.12	1	$\leq 0.004$ - $>4$	68.0	2.5
Ampicillin	1	$>16$	$\leq 0.12$ - $>16$	55.5	31.3
Amoxicillin Clavulanic	0.5	8	$\leq 0.015$ - $>256$	58.3	4.3
Ampicillin Sulbactam	1	16	$\leq 0.015$ - 48	58.5	5.4
Aztreonam	$>32$	$>32$	$\leq 0.06$ - $>32$	34.9	1.6
Ceftriaxone	0.12	64	$\leq 0.03$ - $>64$	74.7	1.1
Clindamycin	0.19	6	$\leq 0.015$ - $>256$	83.3	10.5
Imipenem	$\leq 0.5$	1	$\leq 0.5$ - $>16$	55.5	0.7
Metronidazole	0.75	64	$\leq 0.015$ - $>256$	86.4	12.3
Piperacillin Tazobactam	0.5	2	$\leq 0.015$ - $>64$	67.5	0.2

Interpretive criteria based upon NCCLS published breakpoints. Garenoxacin tentative susceptible breakpoint is defined as  $\leq 4$  mcg/mL all species except *Staphylococcus* spp that are oxacillin or ciprofloxacin resistant which are  $\leq 2$  mcg/ml. Species where breakpoints are not defined by the NCCLS were excluded from the individual drugs calculations.



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Table 3. In vitro Activity of Garenoxacin and Comparators against 456 Clinical Aerobic Pathogens from Pelvic and Gynecological Infections

Antimicrobial	MIC (mcg/mL)			Percent (%)	
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	Sus	Res
<b>Gram Positive Pathogens</b>					
<b>Enterococcus spp (n=66)</b>					
Garenoxacin	0.12	0.25	0.06 - 4	100.0	0.0
Ciprofloxacin	1	1	0.12 - $>4$	93.9	3.0
Ampicillin	1	1	0.5 - $>16$	93.9	6.1
Amoxicillin Clavulanic	0.5	1	0.25 - $>16$	n/a*	n/a*
Ampicillin Sulbactam	1	2	0.5 - $>32$	n/a*	n/a*
Aztreonam	$>32$	$>32$	$>32$ - $>32$	n/a	n/a
Ceftriaxone	64	$>64$	4 - $>64$	n/a*	n/a*
Imipenem	1	1	$<0.5$ - $>16$	n/a	n/a
Piperacillin Tazobactam	2	4	1 - $>64$	n/a*	n/a*
<b>Staphylococcus spp (n=89)</b>					
Garenoxacin	0.05	0.25	0.008 - 8	97.8	0.0
Ciprofloxacin	0.05	2	0.015 - $>4$	91.0	9.0
Ampicillin	1	16	$<0.12$ - $>16$	22.5	77.5
Amoxicillin Clavulanic	0.5	2	$<0.12$ - $>16$	98.9	1.1
Ampicillin Sulbactam	1	2	$<0.25$ - 32	98.9	1.1
Aztreonam	$>32$	$>32$	$>32$ - $>32$	n/a	n/a
Ceftriaxone	4	8	0.5 - $>64$	94.4	1.1
Imipenem	$<0.5$	$<0.5$	$<0.5$ - $>16$	97.8	2.2
Piperacillin Tazobactam	0.5	1	$<0.12$ - $>64$	98.9	1.1
<b>Streptococcus spp (n=99)</b>					
Garenoxacin	0.06	0.12	$<0.004$ - 4	100.0	0.0
Ciprofloxacin	0.5	2	$<0.004$ - $>4$	n/a	n/a
Ampicillin	$<0.12$	0.25	$<0.12$ - 4	92.7	0.0
Amoxicillin Clavulanic	$<0.12$	$<0.12$	$<0.12$ - 2	n/a	n/a
Ampicillin Sulbactam	$<0.25$	$<0.25$	0.03 - 4	n/a	n/a
Aztreonam	$>32$	$>32$	1 - $>32$	n/a	n/a
Ceftriaxone	0.12	0.25	$<0.03$ - 4	97.9	2.1
Imipenem	$<0.5$	$<0.5$	$<0.5$ - $<0.5$	n/a	n/a
Piperacillin Tazobactam	$<0.12$	0.5	0.047 - 16	n/a	n/a
<b>Other Gram Positives (n=39) †</b>					
Garenoxacin	0.06	1	0.015 - $>32$	94.6	2.7
Ciprofloxacin	0.12	4	0.03 - $>4$	n/a	n/a
Ampicillin	0.25	$>16$	$<0.12$ - $>16$	n/a	n/a
Amoxicillin Clavulanic	0.25	4	$<0.12$ - 16	n/a	n/a
Ampicillin Sulbactam	$<0.25$	16	0.12 - 32	n/a	n/a
Aztreonam	$>32$	$>32$	0.25 - $>32$	n/a	n/a
Ceftriaxone	1	64	$<0.03$ - $>64$	n/a	n/a
Imipenem	$<0.5$	1	$<0.5$ - 4	n/a	n/a
Piperacillin Tazobactam	1	8	$<0.12$ - 16	n/a	n/a
<b>Gram Negative Pathogens</b>					
<b>Enterobacteriaceae (n=149)</b>					
Garenoxacin	0.06	0.25	0.008 - 16	98.7	0.7
Ciprofloxacin	0.015	0.03	$<0.004$ - $>4$	99.3	0.7
Ampicillin	8	$>16$	0.5 - $>16$	50.3	45.0
Amoxicillin Clavulanic	4	$>16$	0.5 - $>16$	70.5	15.4
Ampicillin Sulbactam	4	$>32$	0.5 - $>32$	70.5	16.1
Aztreonam	$<0.06$	0.12	$<0.06$ - $>32$	98.7	1.3
Ceftriaxone	$<0.03$	0.12	$<0.03$ - 16	99.3	0.0
Imipenem	$<0.5$	1	$<0.5$ - 2	100.0	0.0
Piperacillin Tazobactam	$<0.12$	2	$<0.12$ - 16	100.0	0.0
<b>Haemophilus spp (n=3)</b>					
Garenoxacin	0.008	0.015	$<0.004$ - 0.015	100.0	0.0
Ciprofloxacin	0.008	0.015	0.008 - 0.015	100.0	0.0
Ampicillin	0.5	2	0.25 - 2	66.7	0.0
Amoxicillin Clavulanic	0.5	2	0.5 - 2	100.0	0.0
Ampicillin Sulbactam	0.5	2	0.5 - 2	100.0	0.0
Aztreonam	0.12	0.12	$<0.06$ - 0.12	100.0	0.0
Ceftriaxone	$<0.03$	$<0.03$	$<0.03$ - $<0.03$	100.0	0.0
Imipenem	1	2	$<0.5$ - 2	100.0	0.0
Piperacillin Tazobactam	$<0.12$	$<0.12$	$<0.12$ - $<0.12$	100.0	0.0
<b>P. aeruginosa &amp; Acinetobacter spp (n=8)</b>					
Garenoxacin	0.06	2	0.015 - 2	100.0	0.0
Ciprofloxacin	0.12	0.5	0.06 - 0.5	100.0	0.0
Ampicillin	$>16$	$>16$	1 - $>16$	n/a	n/a
Amoxicillin Clavulanic	16	$>16$	0.5 - $>16$	n/a	n/a
Ampicillin Sulbactam	2	$>32$	0.5 - $>32$	50.0	50.0
Aztreonam	8	32	2 - 32	62.5	37.5
Ceftriaxone	16	$>64$	0.5 - $>64$	37.5	12.5
Imipenem	$<0.5$	16	$<0.5$ - 16	87.5	12.5
Piperacillin Tazobactam	2	4	$<0.12$ - 4	100.0	0.0
<b>Other Non-Enterobacteriaceae (n=3) ‡</b>					
Garenoxacin	0.5	2	0.03 - 2	100.0	0.0
Ciprofloxacin	0.25	2	0.12 - 2	66.7	0.0
Ampicillin	$>16$	$>16$	$<0.12$ - $>16$	n/a	n/a
Amoxicillin Clavulanic	$>16$	$>16$	$<0.12$ - $>16$	n/a	n/a
Ampicillin Sulbactam	$>32$	$>32$	$<0.25$ - $>32$	33.3	66.7
Aztreonam	$>32$	$>32$	8 - $>32$	33.3	66.7
Ceftriaxone	8	64	8 - 64	66.7	33.3
Imipenem	$<0.5$	8	$<0.5$ - 8	66.7	0.0
Piperacillin Tazobactam	8	16	$<0.12$ - 16	100.0	0.0

\* Ampicillin is the class representative agent.

† Includes both methicillin-sensitive and -resistant strains. 33% of all *Staphylococcus* strains were oxacillin positive.

‡ Includes *Bacillus*, *Corynebacterium*, *Lactobacillus* and *Listeria* spp.

§ Includes *Alcaligenes* and *Stenotrophomonas* strains.

n/a Breakpoints undefined by NCCLS, otherwise, all interpretive criteria are based upon NCCLS published breakpoints. Garenoxacin tentative susceptible breakpoint is defined as  $\leq 4$  mcg/mL all species except *Staphylococcus* spp that are oxacillin or ciprofloxacin resistant which are  $\leq 2$  mcg/ml.

Table 4. In vitro Activity of Garenoxacin and Comparators against 162 Clinical Anaerobic Pathogens from Pelvic and Gynecological Infections

Antimicrobial	MIC (mcg/mL)			Percent (%)	
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	Sus	Res
<b>Gram Positive Anaerobes (n=80)</b>					
Garenoxacin	0.12	0.38	0.004 - 6	98.8	0.0
Amoxicillin Clavulanic	0.047	0.38	$<0.015$ - 16	97.5	1.3
Ampicillin Sulbactam	0.047	0.5	$<0.015$ - 48	97.5	2.5
Clindamycin	0.5	8	$<0.015$ - $>256$	78.8	10.0
Metronidazole	1	$>256$	0.047 - $>256$	80.0	18.8
Piperacillin Tazobactam	0.06	0.5	$<0.015$ - 24	100.0	0.0
<b>Gram Negative Anaerobes (n=82)</b>					
Garenoxacin	0.38	1.5	0.03 - 3	100.0	0.0
Amoxicillin Clavulanic	0.38	2	$<0.015$ - $>256$	98.8	1.2
Ampicillin Sulbactam	0.5	2	$<0.015$ - 16	98.8	0.0
Clindamycin	0.047	6	$<0.015$ - $>256$	87.8	11.0
Metronidazole	0.5	4	$<0.015$ - $>256$	92.7	6.1
Piperacillin Tazobactam	$<0.015$	1.5	$<0.015$ - 32	100.0	0.0

Interpretive criteria based upon NCCLS published breakpoints. Garenoxacin tentative susceptible breakpoint is defined as  $\leq 4$  mcg/ml for anaerobes. Species where breakpoints are not defined by the NCCLS were excluded from the individual drugs listed.

## Conclusions

» Garenoxacin, with a MIC<sub>90</sub> of 0.5mcg/mL, was the most active antimicrobial agent in vitro against all 618 aerobic and anaerobic clinical pathogens from gynecological and pelvic sources in this study.

» Garenoxacin in vitro activity against anaerobic pathogens was comparable to the beta-lactam and beta-lactamase inhibitor compounds and greater than the activity of both clindamycin and metronidazole, with greater than 98% of all pelvic and gynecological strains inhibited at 4 mcg/mL.

» From the activity of garenoxacin in this study, garenoxacin appears to be an excellent empiric choice for both complicated and uncomp