

Comparison *In Vitro* Activity of Garenoxacin (BMS-284756) Against 706 Clinical Aerobes Isolated From Complicated Skin and Skin Structure Infections

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Revised Abstract

Background Garenoxacin (BMS-284756), a des-fluoro (6) quinolone, is a novel fluoroquinolone in development which has shown high activity against many aerobes. 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 complicated skin and skin structure infections as part of a multi-national clinical study. **Methods** Each isolate was identified using selective growth media and various biochemical profiles. The activity of garenoxacin was compared to other relevant compounds. Susceptibility testing was performed using broth microdilution following NCCLS guidelines. Garenoxacin interpretive criteria based on ≤ 4 mcg/mL, susceptible; 8 mcg/mL intermediate; ≥ 16 mcg/mL resistant. **Results** Garenoxacin was the most potent *in vitro* agent evaluated with 98.7% of all isolates tested susceptible (MIC₅₀ 0.6 mcg/mL; MIC₉₀ 2 mcg/mL).

Additional activity is listed in the following table.

Antibiotic	Methicillin Sensitive <i>S. aureus</i> (MSSA) n = 181		Methicillin Resistant <i>S. aureus</i> (MRSA) n = 42		<i>Streptococcus</i> spp n = 150		<i>Enterobacteriaceae</i> n = 134	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Garenoxacin	0.03	0.06	0.03	2	0.06	0.12	0.06	0.5
Amox/Clav	1	1	8	8	≤ 0.12	≤ 0.12	4	> 16
Ampicillin	8	> 16	> 16	> 16	≤ 0.12	≤ 0.12	16	> 16
Aztreonam	> 32	> 32	> 32	> 32	> 32	> 32	≤ 0.06	0.25
Ceftriaxone	2	4	16	32	≤ 0.06	0.25	≤ 0.06	0.25
Ciprofloxacin	0.25	0.5	0.5	> 4	0.5	1	0.015	0.06
Clindamycin	0.12	0.25	0.25	> 16	0.06	1	> 16	> 16
Imipenem	≤ 0.5	≤ 0.5	≤ 0.5	≤ 0.5	≤ 0.5	≤ 0.5	≤ 0.5	2
Pip/Tazo	1	1	16	64	0.12	0.25	1	2

Conclusion Garenoxacin shows excellent anti-staphylococcal and streptococcal activity while retaining significant gram-negative coverage for pathogens common to complicated skin and skin structure infections.

Background

Skin and skin structure infections (SSSIs) are frequently problems for empirical therapy because of the wide variety of Gram-positive and Gram-negative pathogens involved. The most common species isolated in SSSIs are *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus pyogenes*, and because uncomplicated SSSIs rarely lead to systemic infection or integument breakdown, oral antimicrobials with good Gram-positive coverage are frequently employed with good clinical response. Complicated SSSIs may involve a multiplicity of organisms such as *Pseudomonas aeruginosa*, *Enterococcus* spp, *Escherichia coli* and various other enterobacteriaceae, staphylococci and streptococci that often require empiric treatment with broader spectrum antimicrobials [1]. The problem of choice of therapies is frequently made more difficult by the presence of resistant organisms or mixed polymicrobial infections.

Garenoxacin is novel des-fluoro (6) quinolone distinguished from other fluoroquinolones by the absence of a fluorine atom in the six-position. Early studies show that garenoxacin, like older fluoroquinolones, retains

good Gram-negative activity and, like newer extended spectrum fluoroquinolones, has good Gram-positive activity even against organisms that may be resistant to other quinolones [2].

Surveillance studies have shown garenoxacin to be effective against organisms associated with SSSIs [3]. The purpose of this study was to prospectively determine the activity of garenoxacin against pathogens isolated from patients with documented complicated SSSIs in a large multi-center, multi-national clinical study.

Materials and Methods

- All isolates were yielded from complicated skin and skin structure infections according to a phase III clinical trial protocol.
- Clinical isolates were collected between 2001 – 2002 from 55 laboratories as part of a multi-national clinical study.
- Isolates were identified to genus and species at each site and confirmed by the central laboratory.
- Organism collection, transport, confirmation of organism identification, antimicrobial susceptibility testing, as well as, development and management of a centralized database was coordinated by

Laboratories International for Microbiology Studies (LIMS).

Antimicrobial Susceptibility Testing

- MIC's were determined by the central laboratory using broth microdilution panels manufactured by Dade Microscan (Dade Behring Inc., Sacramento, CA, USA) according to NCCLS guidelines and manufacturers instructions [4].
- Quality Control 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.

Results

Results of the study are contained in the following tables.

Table 2. In Vitro Activity (mcg/mL) of Garenoxacin and Comparators Against 534 Gram-positive Aerobic Species from Skin and Skin Structure Infections

Species	Drug	MICs (mg/mL)			% Sus	
		MIC Range	MIC ₅₀	MIC ₉₀		
Gram-positive Species						
<i>Staphylococcus aureus</i> , MSSA (n=181)	Garenox	0.008 - 2	0.03	0.06	100.0	
	Amox/Clav	≤ 0.12 - 8	1	1	99.4	
	Amp	≤ 0.12 - > 16	8	> 16	21.5	
	Ceftriaxone	1 - 32	2	4	99.4	
	Cipro	0.06 - > 4	0.25	0.5	96.7	
	Clinda	0.12 - > 16	0.12	0.25	97.8	
	Imipenem	≤ 0.5 - > 16	≤ 0.5	≤ 0.5	99.4	
	Pip/Tazo	0.25 - 16	1	1	98.9	
	<i>Staphylococcus aureus</i> , MRSA (n=42)	Garenox	0.008 - 4	0.03	2	90.5
		Amox/Clav	1 - > 16	8	8	45.2
Amp		2 - > 16	> 16	> 16	0.0	
Ceftriaxone		2 - > 32	16	32	23.8	
Cipro		0.06 - > 4	0.5	> 4	57.1	
Clinda		0.12 - > 16	0.25	> 16	78.6	
Imipenem		≤ 0.5 - > 16	≤ 0.5	≤ 0.5	92.9	
Pip/Tazo		1 - 64	16	64	47.6	
<i>Staphylococcus epidermidis</i> (n=50)		Garenox	0.015 - 32	0.06	2	98.0
		Amox/Clav	≤ 0.12 - 4	0.5	2	100.0
	Amp	≤ 0.12 - > 16	2	16	16.0	
	Ceftriaxone	0.25 - 32	1	16	82.0	
	Cipro	0.06 - > 4	0.12	> 4	74.0	
	Clinda	0.06 - > 16	0.12	> 16	75.5	
	Imipenem	≤ 0.5 - 8	≤ 0.5	1	98.0	
	Pip/Tazo	≤ 0.12 - 4	0.25	1	100.0	
	<i>Staphylococcus</i> spp (n=65)	Garenox	0.015 - 16	0.06	4	93.8
		Amox/Clav	≤ 0.12 - > 16	0.25	8	89.2
Amp		≤ 0.12 - > 16	0.5	> 16	41.5	
Ceftriaxone		0.25 - > 32	4	32	72.3	
Cipro		0.06 - > 4	0.25	> 4	75.4	
Clinda		0.06 - > 16	0.12	> 16	87.5	
Imipenem		≤ 0.5 - > 16	≤ 0.5	≤ 0.5	93.8	
Pip/Tazo		≤ 0.12 - > 64	0.5	16	89.2	
<i>Enterococcus</i> spp (n=46)		Garenox	0.06 - 4	0.25	2	100.0
		Amox/Clav	0.5 - > 16	0.5	1	na
	Amp	0.5 - > 16	1	1	97.8	
	Ceftriaxone	8 - > 32	> 32	> 32	na	
	Cipro	0.25 - > 4	1	> 4	67.4	
	Clinda	2 - > 16	16	> 16	na	
	Imipenem	≤ 0.5 - > 16	1	2	na	
	Pip/Tazo	1 - > 64	2	4	na	
	<i>Streptococcus pyogenes</i> (n=36)	Garenox	0.06 - 1	0.06	0.25	100.0
		Amox/Clav	≤ 0.12 - 1	≤ 0.12	≤ 0.12	na
Amp		≤ 0.12 - 1	≤ 0.12	≤ 0.12	97.2	
Ceftriaxone		≤ 0.06 - 16	≤ 0.06	0.12	97.2	
Cipro		0.12 - 4	0.5	1	na	
Clinda	0.06 - > 16	0.06	0.12	94.4		

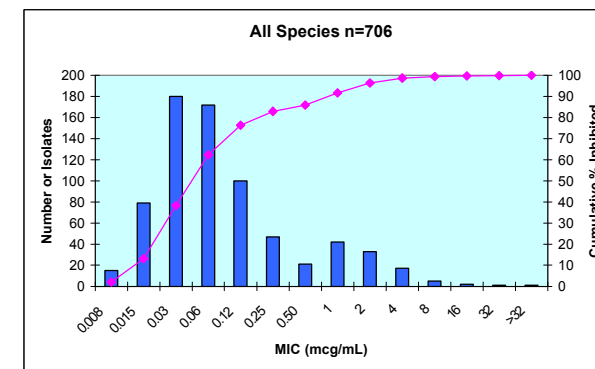
Interpretive criteria based upon NCCLS published breakpoints [5]. Garenoxacin tentative susceptible breakpoint is defined as ≤ 4 mcg/mL all species except MRSA which is ≤ 2 mcg/mL

Table 2. In Vitro Activity (mcg/mL) of Garenoxacin and Comparators Against 172 Gram-negative Aerobic Species from Skin and Skin Structure Infections

Species	Drug	MICs (mg/mL)			% Sus
		MIC Range	MIC ₅₀	MIC ₉₀	
Gram-negative Species					
<i>Escherichia coli</i> (n=42)	Garenox	0.015 - 16	0.03	0.06	97.6
	Amox/Clav	1 - > 16	4	16	83.3
	Amp	1 - > 16	4	> 16	64.3
	Aztreonam	≤ 0.06 - 0.5	≤ 0.06	0.12	100.0
	Ceftriaxone	≤ 0.06 - 0.12	≤ 0.06	0.12	100.0
	Cipro	0.008 - > 4	0.015	0.015	97.6
	Imipenem	≤ 0.5 - 1	≤ 0.5	≤ 0.5	100.0
	Pip/Tazo	0.5 - 4	1	2	100.0
<i>Klebsiella</i> spp (n=28)	Garenox	0.03 - 0.12	0.12	0.12	100.0
	Amox/Clav	1 - 4	2	4	100.0
	Amp	8 - > 16	> 16	> 16	10.7
	Aztreonam	≤ 0.06 - > 32	≤ 0.06	0.25	96.4
	Ceftriaxone	≤ 0.06 - 2	≤ 0.06	≤ 0.06	100.0
	Cipro	≤ 0.004 - 0.12	0.015	0.03	100.0
	Imipenem	≤ 0.5 - 1	≤ 0.5	1	100.0
	Pip/Tazo	0.5 - 2	1	2	100.0
<i>Proteus</i> spp (n=21)	Garenox	0.12 - 8	0.25	0.5	95.2
	Amox/Clav	0.5 - > 16	1	4	90.5
	Amp	0.5 - > 16	1	> 16	85.7
	Aztreonam	≤ 0.06	≤ 0.06	≤ 0.06	100.0
	Ceftriaxone	≤ 0.06	≤ 0.06	≤ 0.06	100.0
	Cipro	0.008 - 1	0.03	0.03	100.0
	Imipenem	≤ 0.5 - > 16	2	4	95.2
	Pip/Tazo	≤ 0.12 - 4	0.25	0.25	100.0
Other Enterobacteriaceae (n=43)	Garenox	0.03 - 2	0.12	1	100.0
	Amox/Clav	2 - > 16	> 16	> 16	16.3
	Amp	2 - > 16	> 16	> 16	25.6
	Aztreonam	≤ 0.06 - > 32	≤ 0.06	0.5	95.3
	Ceftriaxone	≤ 0.06 - 32	0.12	1	95.3
	Cipro	0.008 - 0.5	0.015	0.12	100.0
	Imipenem	≤ 0.5 - 4	≤ 0.5	2	100.0
	Pip/Tazo	0.25 - 8	1	2	100.0
<i>Pseudomonas aeruginosa</i> (n=38)	Garenox	0.5 - > 32	1	4	94.7
	Amox/Clav	16 - > 16	> 16	> 16	na
	Amp	> 16	> 16	> 16	na
	Aztreonam	0.12 - > 32	8	8	92.1
	Ceftriaxone	0.5 - > 32	32	> 32	18.4
	Cipro	0.06 - > 4	0.12	1	94.7
	Imipenem	≤ 0.5 - > 16	1	> 16	86.8
	Pip/Tazo	1 - 64	4	8	100.0

Interpretive criteria based upon NCCLS published breakpoints [5]. Garenoxacin tentative susceptible breakpoint is defined as ≤ 4 mcg/mL.

Figure 1. In Vitro Activity of Garenoxacin Against 706 Clinical Isolates from Skin and Skin Structure Infections



Conclusions

- The MIC₉₀ of garenoxacin was 1 mcg/mL against all isolates from complicated SSSIs.
- Garenoxacin inhibited 98.7% of all SSSI isolates at 4 mcg/mL.
- Garenoxacin had an MIC₉₀ of 2 mcg/ml against MRSA and all *Enterococcus* spp.
- Only imipenem had MICs consistently equal to or lower than garenoxacin against Gram-positive organisms from the SSSIs in this study.
- Interpretive susceptibility data demonstrate garenoxacin activity comparable to ciprofloxacin against *E. coli*, *Klebsiella* spp, and *P. aeruginosa*.
- Garenoxacin (MIC₉₀ 0.5 mcg/mL) was slightly less active against *Proteus* spp when compared to aztreonam (≤ 0.06), ceftriaxone (≤ 0.06), ciprofloxacin (0.03) and piperacillin/tazobactam (0.25).
- The data in this study demonstrates that garenoxacin has potent *in vitro* activity against both Gram-positive and Gram-negative pathogens associated with SSSIs.

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