In Vitro Activity of Garenoxacin, a Novel Des-F(6)-Quinolone, and Other Orally Administered Antimicrobials Tested Against 50,217 Enterobacteriaceae Collected Worldwide by the SENTRY Antimicrobial Surveillance Program (1999-2003)

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Abstract

Objective: To compare the activity of garenoxacin (GRN; formerly BMS284756) with selected antimicrobials against a worldwide collection of Enterobacteriaceae (ENT). GRN, unlike recently marketed fluoroquinolones (FQ), lacks fluorine at the C-6 position.
Methods: The isolates were consecutively collected from > 70 medical centers from bloodstream, respiratory, urinary and skin and soft tissue infections and tested by reference broth microdilution methods according to NCCLS guidelines. A GRN susceptible (S) breakpoint of ≤ 2 mg/L was applied for comparison purposes only.
Results: The results of the major organism groups tested follows:

		% S				
Organism (no. tested)	GRN (MIC_{50}/% S)	Ciprofloxacin	Levofloxacin	Amox/Clav	Cefuroxime	TMP/SMX[a]
E. coli (22,698)	≤0.03/87	87	88	81	76	76
Klebsiella spp. (10,513)	0.12/90	91	92	80	71	86
Enterobacter spp. (5,759)	0.12/86	88	90	4	21	89
Salmonella spp. (2,985)	0.06/99	99	99	89	62	92
P. mirabilis (2,391)	0.5/78	83	89	91	91	80
Serratia spp. (2,385)	1/75	89	93	3	1	91
Citrobacter spp. (1,206)	0.12/87	90	92	40	57	90
Indole-pos. *Proteae* (1,109)	0.5/74	80	82	23	16	80
Shigella spp. (787)	≤0.03/>99.9	100	100	65	96	32
Total (50,217)	0.06/87	89	90	67	63	81

a. TMP/SMX = trimethoprim/sulfamethoxazole.

GRN showed excellent activity against this large collection of ENT (MIC_{50}, 0.06 mg/L) and 87% of isolates were inhibited at ≤ 2 mg/L. The in vitro activity of GRN was similar to that of ciprofloxacin (CIP) against most ENT species, the exceptions were *Serratia* and indole-positive Proteae where CIP was slightly more active. In general GRN and CIP showed higher potency and a broader spectrum than orally administered ß-lactams or TMP/SMX. GRN was also highly active against *E. coli* O157:H7 and *Yersinia enterocolitica* (MIC_{50}, 0.25 mg/L for both).
Conclusions: GRN in vitro activity was similar to that of the most commonly used FQs and superior to other listed orally administered antimicrobials when tested against over 50,000 global ENT isolates.

Introduction

The number of drug resistant Enterobacteriaceae isolates has markedly increased in the last two decades. For example, there has been an increase in the number of stably derepressed AmpC producing strains among *Citrobacter freundii*, *Enterobacter* spp. and *Serratia marcescens* isolates, usually selected by overuse of "third-generation" cephalosporins (ceftriaxone or ceftazidime). Also the rapid emergence and dissemination of extended spectrum ß-lactamases (ESBL) in *Escherichia coli* and *Klebsiella* spp. isolates have required greater usage of ß-lactamase-stable carbapenems such as imipenem and meropenem. Some ESBL types (CTX-M) are associated with co-resistance to fluoroquinolones, agents that are regarded as alternative treatments. As new/novel fluoroquinolones are developed, they must be assessed against these enteric species to determine their role in contemporary chemotherapy.

Garenoxacin (formerly T-3811ME or BMS-284756) is a novel des-F(6)-quinolone that lacks the C6-position fluorine and has a unique difluoromethoxy substitution at position C8. These alterations result in a drug with improved potency against both DNA gyrase and topoisomerase IV. Garenoxacin has been described as highly active against important Gram-positive and -negative pathogens including: Enterobacteriaceae, staphylococci, streptococci (*S. pneumoniae*, viridans group species, and ß-haemolytic streptococci), *Acinetobacter* spp. and some other Gram-negative non-fermentative bacilli, *Haemophilus influenzae*, *Moraxella catarrhalis*, atypical respiratory tract pathogens (Mycoplasmas, *C. pneumoniae*, and *Legionella* spp.), many enterococci and anaerobes, especially Gram-positive species. These features are complimented by the high probability of favorable target attainment (AUC/MIC) that has been associated with successful bacterial eradication and minimization of mutational events among indicated species (i.e. low MPC values). These elements of spectrum and potency favor garenoxacin applications for 1) community-acquired respiratory tract infections (CA-RTI; hospitalized or ambulatory patients); 2) skin and soft tissue infections (complicated with mixed flora or uncomplicated); and 3) selected community-acquired intra-abdominal infection indications.

The in vitro testing results for garenoxacin from the SENTRY Antimicrobial Surveillance Program were summarized from 1999 onward to assess the spectrum and potency versus a very large collection of Enterobacteriaceae. A total of 50,217 isolates were analyzed from results generated by the reference (National Committee for Clinical Laboratory Standards [NCCLS], currently the Clinical Laboratory Standards Institute [CLSI]) methods as described in document M7-A6 [2003].

Materials and Methods

Susceptibility testing. All MIC values were generated using broth microdilution methods (CLSI/NCCLS, M6-A7) in panels produced by TREK Diagnostics (Cleveland, Ohio, USA). Mueller-Hinton broth was supplemented where indicated with 2 - 5% lysed horse blood (fastidious species including streptococci) and HTM components (*Haemophilus* species). The following CLSI/NCCLS-recommended quality control (QC) strains were routinely tested: *E. coli* ATCC 25922 and 35218; *P. aeruginosa* ATCC 27583; *E. faecalis* ATCC 29212; *S. aureus* ATCC 25923 and 29213; *H. influenzae* ATCC 49247 and 49766; and *S. pneumoniae* ATCC 49619. All QC results were within published ranges (CLSI/NCCLS, M100-S15). Approximately 35 - 40 different antimicrobial agents were processed each year with selected agents compared to garenoxacin in this presentation. A garenoxacin susceptible breakpoint of ≤ 2 mg/L was used for comparison purposes only.

Bacterial strains. The organisms were processed in three central laboratories (JMI Laboratories, North Liberty, Iowa, USA; Women's and Children's Hospital, Adelaide, Australia; Utrecht University, Utrecht, The Netherlands) using common reference test reagents. Isolates were derived from a wide variety of clinical sources (Program Objectives) such as bloodstream (BSI), community-acquired or nosocomial respiratory tract sites (RTI), skin and soft tissue infections (SSTI), urinary tract infections (UTI) and selected patient populations. In this investigation the 50,217 isolates were consecutively collected from a wide variety of infections at medical centers in North America (≥ 30 sites in the USA and Canada), Latin America (10 sites), Europe (≥ 30 sites) and the Asia-Pacific region (nine nations plus South Africa).

Table 1 lists these groups in rank order with *E. coli* (45.2%), *Klebsiella* species (20.9%; six species mainly *K. oxytoca* [1,679] and *K. pneumoniae* [8,566]), and *Enterobacter* spp. (11.5%; nine species principally *E. aerogenes* [1,282] and *E. cloacae* [4,011]) accounting for 77.6% of all processed isolates. Among the 208 other bacterial isolates, these organisms had more than 10 strains identified over the five-year interval: other *Escherichia* species (44), *Hafnia alvei* (70), *Kluyvera* spp. (16), *Leclercia* spp. (10), *Proteus penneri* (21), and *Yersinia enterocolitica* (47).

Results

- Table 1 lists the most commonly isolated Enterobacteriaceae from the SENTRY Program. *E. coli* was clearly the most important pathogen followed by various *Klebsiella* spp. (20.9%) and *Enterobacter* spp. (11.5%).
- Among the 22,698 *E. coli* isolates tested against garenoxacin, several resistance mechanisms were noted including: ESBLs (4.3 - 5.3% phenotypes; approximately 25% confirmed); non-ESBL enzymes, aminoglycoside inactivating enzymes and fluoroquinolone resistances (9.2 – 12.5%) secondary to QRDR mutations. All fluoroquinolones tested had a similar coverage (% susceptible) for *E. coli* (87.2 - 87.7%).
- Garenoxacin inhibition of *Klebsiella* spp. and *Enterobacter* spp. at ≤ 2 mg/L was comparable to ciprofloxacin, gatifloxacin and levofloxacin, but superior to gemifloxacin. ESBL phenotypes were more prevalent among *Klebsiella* spp. (17.7 - 18.4%) compared to other Enterobacteriaceae tested.
- *Salmonella* spp. (2,985 isolates) and *Shigella* spp. (787 isolates) were highly susceptible (≥ 98.4%) to all tested fluoroquinolones (Table 2). Resistance rates for all classes generally were at ≤ 1%.
- Garenoxacin and gemifloxacin were less active than the comparator fluoroquinolones against *P. mirabilis* (77.1 - 77.7% susceptible), indole-positive *Proteae* (73.5 - 73.8%) and *Serratia* spp. (75.1 - 75.3%).
- 86.6% of *Citrobacter* spp. (Table 2) were susceptible to garenoxacin (MIC ≤ 2 mg/L), this frequency was comparable or superior to other fluoroquinolones, cephalosporins (except cefepime) and piperacillin/tazobactam. Only gentamicin, imipenem, and cefepime exhibited superior rates of susceptibility.
- *Pantoea* spp. isolates were generally very susceptible to all tested agents (> 90% susceptibility) except amoxicillin/clavulanate, cefoxitin and cefuroxime.
- Table 3 lists the activity of six fluoroquinolones against all Enterobacteriaceae. Using either the published (CLSI/NCCLS) or proposed breakpoints (GRN) the susceptibility rates ranged from 86.3% (gemifloxacin) to 90.0% (levofloxacin), with garenoxacin at 87.4% (≤ 2 mg/L). Projected adjustments in fluoroquinolone breakpoints guided by PK/PD parameters could alter this perception.

Table 1. Distribution of Enterobacteriaceae genera and species tested against garenoxacin (1999 - 2003); 50,217 isolates.

Rank	Species/genus group	No. tested (%)
1	*E. coli*	22,698 (45.2)
2	*Klebsiella spp.*	10,513 (20.9)
3	*Enterobacter spp.*	5,759 (11.5)
4	*Salmonella spp.*	2,985 (5.9)
5	*P. mirabilis*	2,391 (4.8)
6	*Serratia spp.*	2,385 (4.7)
7	*Citrobacter spp.*	1,206 (2.4)
8	*Indole-positive Proteae*	1,109 (2.2)
9	*Shigella spp.*	787 (1.6)
10	*Pantoea spp.*	176 (0.4)
11	Other species	208 (0.4)

Table 3. Cumulative percentage of isolates inhibited by garenoxacin and comparison fluoroquinolones versus 50,217 enteric bacilli (SENTRY Program, 1999 - 2003).

	% inhibited at MIC (mg/L):							
Fluoroquinolone	≤0.03	0.06	0.12	0.25	0.5	1	2	4
Garenoxacin	31.7	51.6	68.8	76.3	81.2	84.9	(87.4)[a]	89.1
Ciprofloxacin	-	-	-	85.3	87.3	(88.8)	89.9	-
Gatifloxacin	55.1	71.3	77.5	83.5	86.5	88.3	(89.9)	92.6
Gemifloxacin	-	-	83.3	(86.3)	88.0	89.4	-	-
Levofloxacin	57.3	75.2	79.8	84.1	86.8	88.7	(90.0)	92.1
Moxifloxacin	27.5	55.9	70.6	77.2	83.4	85.5	86.7	87.9

a. Susceptibility breakpoints are in parenthesis, where available. A breakpoint of ≤ 2 mg/L was applied to garenoxacin for comparison purposes only. No CLSI breakpoint for Enterobacteriaceae testing has been published for moxifloxacin.
b. - = untested concentration.

Table 2. In vitro activity of garenoxacin and 15 comparison agents tested against 50,009 strains of Enterobacteriaceae (SENTRY Program, 1999 - 2003).

	MIC (mg/L)		% by category:[a]	
Organism (rank; no. tested)/antimicrobial agent	50%	90%	Susceptible	Resistant
E. coli (22,698)				
Garenoxacin	≤0.03	>4	87.3[b]	12.3
Ciprofloxacin	≤0.25	>2	87.2	12.5
Gatifloxacin	≤0.03	4	87.7	9.2
Gemifloxacin	≤0.12	>1	87.3	12.1
Levofloxacin	≤0.03	>4	87.6	10.3
Moxifloxacin	0.06	>4	-	-
Amoxicillin/Clavulanate	≤2	16	80.7	5.6
Aztreonam	≤0.12	≤0.12	97.0	2.3(5.3)[d]
Cefepime	≤0.12	≤0.12	98.1	1.5
Cefoxitin	4	8	92.6	3.7
Ceftazidime	≤2	≤2	97.4	1.7(5.1)[d]
Ceftriaxone	≤0.25	≤0.25	96.8	2.5(4.3)[d]
Cefuroxime	4	8	91.3	5.3
Gentamicin	≤2	≤2	92.2	6.9
Imipenem	≤0.5	≤0.5	>99.9	<0.1
Piperacillin/Tazobactam	2	4	96.4	1.8
Klebsiella spp. (10,513)				
Garenoxacin	0.12	2	90.3	7.8
Ciprofloxacin	≤0.25	1	90.6	8.0
Gatifloxacin	0.06	1	92.5	5.0
Gemifloxacin	≤0.12	0.5	87.8	9.8
Levofloxacin	0.06	1	92.2	5.5
Moxifloxacin	0.12	4	-	-
Amoxicillin/Clavulanate	≤2	16	80.1	8.8
Aztreonam	≤0.12	>16	84.6	14.8(18.4)[d]
Cefepime	≤0.12	1	91.4	4.8
Cefoxitin	8	16	88.2	6.6
Ceftazidime	≤2	>16	86.7	11.3(17.7)[d]
Ceftriaxone	≤0.25	32	85.8	9.0(18.2)[d]
Cefuroxime	2	>16	77.7	17.9
Gentamicin	≤2	>8	86.3	12.4
Imipenem	≤0.5	≤0.5	99.9	0.1
Piperacillin/Tazobactam	2	64	87.6	9.2
Enterobacter spp. (5,759)				
Garenoxacin	0.12	>4	86.2	11.1
Ciprofloxacin	≤0.25	>2	87.8	10.3
Gatifloxacin	≤0.03	4	89.9	7.6
Gemifloxacin	≤0.12	>1	83.8	13.2
Levofloxacin	≤0.03	4	89.6	8.5
Moxifloxacin	0.12	>4	-	-
Amoxicillin/Clavulanate	>16	>16	4.3	93.0
Aztreonam	≤0.12	>16	73.5	21.1
Cefepime	≤0.12	>32	75.5	21.2
Cefoxitin	>32	>32	5.9	94.2
Ceftazidime	≤2	>16	71.9	23.7
Ceftriaxone	≤0.25	>32	75.0	14.3
Cefuroxime	16	>16	44.4	43.4
Gentamicin	≤2	>8	88.4	10.3
Imipenem	≤0.5	1	99.7	0.2
Piperacillin/Tazobactam	2	>64	77.1	10.5
Salmonella spp. (2,985)				
Garenoxacin	0.06	0.25	99.0	0.8
Ciprofloxacin	≤0.25	≤0.25	99.2	0.7
Gatifloxacin	≤0.03	0.25	99.3	0.6
Gemifloxacin	≤0.12	≤0.12	98.4	0.8
Levofloxacin	0.06	0.25	99.2	0.7
Moxifloxacin	0.12	0.5	-	-
Amoxicillin/Clavulanate	≤2	16	88.6	2.9
Aztreonam	≤0.12	≤0.12	98.8	0.6
Cefepime	≤0.12	≤0.12	99.5	0.1
Cefoxitin	4	8	98.3	1.1
Ceftazidime	≤2	≤2	99.2	0.6
Ceftriaxone	≤0.25	≤0.25	99.2	0.5
Cefuroxime	4	8	94.7	1.9
Gentamicin	≤2	≤2	97.1	2.1
Imipenem	≤0.5	≤0.5	100.0	0.0
Piperacillin/Tazobactam	2	4	97.8	1.3
P. mirabilis (2,391)				
Garenoxacin	0.5	>4	77.7	20.6
Ciprofloxacin	≤0.25	>2	82.6	22.9
Gatifloxacin	0.12	>4	83.5	11.0
Gemifloxacin	≤0.12	>1	77.1	22.3
Levofloxacin	0.06	4	88.6	7.9
Moxifloxacin	0.25	>4	-	-
Amoxicillin/Clavulanate	≤2	8	91.3	3.4
Aztreonam	≤0.12	≤0.12	98.7	0.8(4.3)[d]
Cefepime	≤0.12	0.25	96.0	3.0
Cefoxitin	4	4	96.7	1.6
Ceftazidime	≤2	≤2	95.5	4.5(3.4)[d]
Ceftriaxone	≤0.25	≤0.25	94.6	3.5(6.7)[d]
Cefuroxime	1	4	92.1	7.7
Gentamicin	≤2	>8	87.7	10.4
Imipenem	1	2	99.7	<0.1
Piperacillin/Tazobactam	≤0.5	1	98.8	0.8
Serratia spp. (2,385)				
Garenoxacin	1	>4	75.1	13.5
Ciprofloxacin	≤0.25	2	88.5	7.6
Gatifloxacin	0.25	2	91.6	5.1
Gemifloxacin	≤0.12	>1	75.3	17.8
Levofloxacin	0.12	2	92.5	5.3
Moxifloxacin	0.5	4	-	-
Amoxicillin/Clavulanate	>16	>16	3.2	93.9
Aztreonam	≤0.12	4	92.0	6.8
Cefepime	≤0.12	1	95.8	2.9
Cefoxitin	16	>32	14.0	42.7
Ceftazidime	≤2	≤2	94.0	5.0
Ceftriaxone	≤0.25	2	89.4	7.7
Cefuroxime	>16	>16	2.1	93.7
Gentamicin	≤2	8	87.8	9.6
Imipenem	≤0.5	2	99.4	0.3
Piperacillin/Tazobactam	2	32	88.7	3.0
Citrobacter spp. (1,206)				
Garenoxacin	0.12	4	86.8	9.9
Ciprofloxacin	≤0.25	1	90.3	7.5
Gatifloxacin	≤0.03	2	91.8	4.6
Gemifloxacin	≤0.12	1	85.7	11.7
Levofloxacin	≤0.03	2	91.9	5.1
Moxifloxacin	0.12	>4	-	-
Amoxicillin/Clavulanate	>16	>16	40.0	51.7
Aztreonam	≤0.12	>16	83.7	12.4
Cefepime	≤0.12	1	98.7	1.1
Cefoxitin	>32	>32	38.0	58.3
Ceftazidime	≤2	>16	82.4	14.9
Ceftriaxone	≤0.25	32	84.1	6.2
Cefuroxime	4	>16	70.0	24.6
Gentamicin	≤2	≤2	92.0	6.7
Imipenem	0.5	1	>99.9	<0.1
Piperacillin/Tazobactam	2	32	86.5	4.9
Indole-positive *Proteae* (1,109)				
Garenoxacin	0.5	>4	73.8	21.2
Ciprofloxacin	≤0.25	>2	79.9	17.5
Gatifloxacin	0.12	>4	81.4	15.4
Gemifloxacin	≤0.12	>1	73.5	25.0
Levofloxacin	0.06	>4	81.9	13.9
Moxifloxacin	0.25	>4	-	-
Amoxicillin/Clavulanate	>16	>16	22.9	74.1
Aztreonam	≤0.12	1	97.0	1.8
Cefepime	≤0.12	0.25	97.8	1.0
Cefoxitin	8	16	66.3	9.0
Ceftazidime	≤2	8	92.0	4.5
Ceftriaxone	≤0.25	4	96.1	2.3
Cefuroxime	>16	>16	20.1	68.3
Gentamicin	≤2	>8	85.5	11.1
Imipenem	2	4	99.5	0.0
Piperacillin/Tazobactam	≤0.5	4	97.9	0.5
Shigella spp. (787)				
Garenoxacin	≤0.03	≤0.03	99.9	0.0
Ciprofloxacin	≤0.25	≤0.25	100.0	0.0
Gatifloxacin	≤0.03	≤0.03	100.0	0.0
Gemifloxacin	≤0.12	≤0.12	99.7	0.0
Levofloxacin	≤0.03	≤0.03	100.0	0.0
Moxifloxacin	≤0.03	0.06	-	-
Amoxicillin/Clavulanate	8	16	65.4	1.1
Aztreonam	≤0.12	≤0.12	99.7	0.3
Cefepime	≤0.12	0.25	99.9	0.1
Cefoxitin	2	4	99.7	0.1
Ceftazidime	≤2	≤2	99.7	0.3
Ceftriaxone	≤0.25	≤0.25	99.7	0.3
Cefuroxime	2	4	99.6	0.3
Gentamicin	≤2	≤2	99.9	0.1
Imipenem	≤0.5	≤0.5	100.0	0.0
Piperacillin/Tazobactam	2	4	99.9	0.1
Pantoea spp. (176)				
Garenoxacin	0.06	0.5	95.5	3.4
Ciprofloxacin	≤0.25	≤0.25	97.2	2.8
Gatifloxacin	≤0.03	0.12	97.2	2.3
Gemifloxacin	≤0.12	≤0.12	95.2	4.2
Levofloxacin	≤0.03	0.12	97.2	2.3
Moxifloxacin	0.06	0.12	-	-
Amoxicillin/Clavulanate	8	>16	72.7	22.7
Aztreonam	≤0.12	8	90.3	8.0
Cefepime	≤0.12	2	99.4	0.6
Cefoxitin	16	>32	47.7	33.0
Ceftazidime	≤2	4	93.2	6.8
Ceftriaxone	≤0.25	8	90.9	3.4
Cefuroxime	8	>16	71.6	17.6
Gentamicin	≤2	≤2	94.6	2.8
Imipenem	≤0.5	≤0.5	99.4	0.6
Piperacillin/Tazobactam	2	4	95.4	2.9

a. Susceptibility criteria of CLSI (2005), where available.
b. Susceptibility defined as ≤ 2 mg/L for garenoxacin for comparison purposes only.
c. - = no susceptibility criteria available (CLSI, 2005).
d. Percentage in parenthesis indicates the proportion of strains with an ESBL phenotype.

Conclusions

- Garenoxacin, when tested against over 50,000 recent (1999 - 2003) clinical isolates of Enterobacteriaceae, demonstrated a potency and spectrum comparable to that of currently marketed fluoroquinolones such as ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin and moxifloxacin.
- MIC_{50} values for garenoxacin ranged from ≤ 0.03 mg/L (*E. coli* and *Shigella* spp.) to 1 mg/L (*Serratia* spp.). Percentage susceptibility for the five most prevalent species or genus groups (Table 1 and 2) was 78 to 99%.
- Overall, 87.4% of Enterobacteriaceae pathogens (1999 - 2003) had a garenoxacin MIC of ≤ 2 mg/L. This compares favorably to ciprofloxacin (88.8% at ≤ 1 mg/L) and gemifloxacin (86.3% at ≤ 0.25 mg/L) using CLSI/NCCLS breakpoints.
- Garenoxacin is a novel quinolone compound with a potential role in the treatment of contemporary isolates of enteric bacilli.

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