

# In Vitro Activity of the Novel Des-F(6)-Quinolone, Garenoxacin, Against 27,831 Community-Acquired Respiratory Tract Infection Pathogens: Report from the SENTRY Antimicrobial Surveillance Program (1999-2002)

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## ABSTRACT

**Background:** The in vitro activity of garenoxacin (GRN), formerly BMS284756, in comparison to gatifloxacin (GAT), levofloxacin (LEV) and ciprofloxacin (CIP) was assessed against a large collection of CARTI pathogens.

**Methods:** The isolates were consecutively collected as part of the SENTRY Program in North America (NA; 51%), Europe (EU; 28%), Asia-Pacific (AP; 11%) and Latin America (LA; 10%), and included *S. pneumoniae* (SPN; 12,461 isolates), *H. influenzae* (HI; 10,769) and *M. catarrhalis* (MCAT; 4,601). The isolates were tested by NCCLS broth microdilution methods. A GRN susceptible (S) breakpoint of  $\leq 2 \mu\text{g/ml}$  was applied for comparison purposes.

**Results:** The results are summarized in the table:

Organism (no. tested)	MIC <sub>90</sub> ( $\mu\text{g/ml}$ )/% S			
	GRN	GAT	LEV	CIP
<b>SPN</b>				
penicillin (PEN)-S (8,500)	0.06/>99.9	0.5/99.5	1/99.4	2/-
PEN-intermediate (1,844)	0.06/100	0.5/99.2	1/99.1	2/-
PEN-resistant (R; 2,117)	0.06/>99.9	0.5/98.5	1/98.1	2/-
<b>HI</b>				
$\beta$ -lactamase (BL)-negative (8,395)	$\leq 0.03$ />99.9	$\leq 0.03$ />99.9	$\leq 0.03$ /100	$\leq 0.03$ />99.9
BL-producers (2,374)	$\leq 0.03$ /100	$\leq 0.03$ /100	$\leq 0.03$ /100	$\leq 0.03$ /100
MCAT (4,601)	$\leq 0.03$ /100	$\leq 0.03$ /100	$\leq 0.03$ /100	$\leq 0.03$ /100

GRN was eight- to 16-fold more potent than GAT or LEV against SPN. R to PEN did not affect GRN or other quinolone (FQ) activity, but the occurrence of R to GAT and LEV was higher among PEN-R strains. Erythromycin (ERY)-R varied from 10.2% among PEN-S to 70.1% among PEN-R strains. GRN was uniformly active against SPN in all regions (>99.9% S), but R to LEV was highest in AP (1.6%), followed by NA (0.9%), EU (0.5%) and LA (0.2%). There was an increase in LEV-R among SPN during the study period (from 0.7% in 1999 to 0.9% in 2002). R to PEN and ERY increased from 1999 (14.4/22.5%) to 2001 (20.0/28.9%), but decreased in 2002 (14.3/23.5%). All FQs were highly active against both HI and MCAT, and independent of BL production.

**Conclusions:** GRN showed higher activity against SPN and similar activity against HI and MCAT when compared to GAT, LEV and CIP. This compound may represent an excellent option for the treatment of CARTI.

## INTRODUCTION

Garenoxacin (formerly BMS 284756 and T-3811) is a novel des-F(6)quinolone. Garenoxacin differs from recently approved quinolones by the lack of a fluorine at the C-6 position, but it has fluorine incorporated through a C-8 difluoromethyl ether linkage. Significant differences in potency and spectrum have been demonstrated among the marketed quinolones.

Garenoxacin has shown enhanced activity against Gram-positive organisms, especially *Streptococcus pneumoniae* and *Staphylococcus aureus*. In addition, garenoxacin activity against *Haemophilus influenzae* and *Moraxella catarrhalis* has been comparable to that of the currently marketed fluoroquinolones.

The SENTRY Antimicrobial Surveillance Program is a worldwide longitudinal study that has been monitoring pathogen susceptibilities and resistance trends since 1997. The purpose of the study was to analyze the activity of garenoxacin in comparison to gatifloxacin, levofloxacin and ciprofloxacin against a large collection of organisms isolated from patients with community-acquired respiratory tract infections (CARTI).

## METHODS

The isolates were consecutively collected from patients with CARTI as part of the SENTRY Program in North America (51% of all strains), Europe (28%), Asia-Pacific and South Africa region (11%) and Latin America (10%); and included *S. pneumoniae* (12,461 isolates), *H. influenzae* (10,769) and *M. catarrhalis* (4,601). Susceptibility tests were performed in two coordinating laboratories. Isolates from North America, Latin America and Europe were tested at the Jones Microbiology Institute (North Liberty, Iowa, USA); while isolates from the Asia-Pacific and South Africa region were tested at the Women's and Children's Hospital (Adelaide, Australia).

The isolates were susceptibility tested by NCCLS reference broth microdilution methods against garenoxacin, gatifloxacin, levofloxacin, ciprofloxacin, and more than 20 comparator agents. Quality control tests and colony counts were routinely performed with *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49766 and 49247, and *Escherichia coli* ATCC 25922 and 35218. A garenoxacin susceptible breakpoint of  $\leq 2 \mu\text{g/ml}$  was applied for comparative purposes only. All other breakpoints utilized were those published by the NCCLS.

## COMMENTS

- Garenoxacin was the most potent quinolone tested against *S. pneumoniae*. Garenoxacin (MIC<sub>50/90</sub>, 0.06  $\mu\text{g/ml}$ ) was 16- and 32-fold more potent than levofloxacin (MIC<sub>50/90</sub>, 1  $\mu\text{g/ml}$ ) or ciprofloxacin, and four- to eight-fold more potent than gatifloxacin (Table 1).
- Penicillin-resistant *S. pneumoniae* (MIC,  $\geq 2 \mu\text{g/ml}$ ) showed higher rates of resistance to either levofloxacin (1.8%) or gatifloxacin (1.5%) when compared to penicillin-susceptible strains (0.5%). In contrast, strains with decreased susceptibility to garenoxacin (MIC,  $>2 \mu\text{g/ml}$ ) were very rare among *S. pneumoniae* strains independently of their susceptibility to penicillin (<0.1%; Table 1).
- All quinolones were highly active (MIC<sub>90</sub>,  $\leq 0.03 \mu\text{g/ml}$ ) against *H. influenzae* and *M. catarrhalis*, regardless of  $\beta$ -lactamase production (Table 1).
- Garenoxacin activity against *S. pneumoniae* did not vary by region or year of isolation (Tables 2 and 3). Levofloxacin-resistance rates were higher in the Asia-Pacific and South Africa region (1.6%) and North America (0.9%) when compared to Europe (0.5%) and Latin America (0.2%).
- Fluoroquinolone resistance rates did not increase markedly among *S. pneumoniae* worldwide during the study period. Levofloxacin-resistance increased from 0.7% in 1999 to 0.9% in 2002.
- Resistance rates to penicillin and erythromycin increased from 1999 (14.4 and 22.5%, respectively) to 2001 (20.0 and 28.9%), but decreased in 2002 (14.3 and 23.5%).

## RESULTS

**Table 1.** In vitro activity of garenoxacin in comparison to other compounds tested against bacterial pathogens from community-acquired respiratory tract infections (SENTRY Program, 1999-2002).

Organism/antimicrobial agent (no. tested)	MIC ( $\mu\text{g/ml}$ )			Category:	
	50%	90%	Range	% susceptible	% resistant
<b><i>S. pneumoniae</i></b>					
<b>penicillin-susceptible (8,500)</b>					
Garenoxacin	0.06	0.06	$\leq 0.03$ -4	>99.9 <sup>a</sup>	<0.1 <sup>a</sup>
Ciprofloxacin	1	2	$\leq 0.25$ ->4	- <sup>b</sup>	-
Levofloxacin	1	1	$\leq 0.03$ ->4	99.4	0.5
Gatifloxacin	0.25	0.5	$\leq 0.03$ ->4	99.5	0.5
Amoxicillin/Clavulanate	$\leq 2$	$\leq 2$	$\leq 2$ ->16	100.0	0.0
Ceftriaxone	$\leq 0.25$	$\leq 0.25$	$\leq 0.25$ -4	99.8	0.1
Clindamycin	$\leq 0.25$	$\leq 0.25$	$\leq 0.25$ ->2	95.3	4.2
Erythromycin	$\leq 0.25$	1	$\leq 0.25$ ->8	89.1	10.2
<b>penicillin-intermediate (1,844)</b>					
Garenoxacin	0.06	0.06	$\leq 0.03$ -2	100.0 <sup>a</sup>	0.0 <sup>a</sup>
Ciprofloxacin	1	2	$\leq 0.25$ ->4	-	-
Levofloxacin	1	1	$\leq 0.03$ ->4	99.1	0.9
Gatifloxacin	0.25	0.5	$\leq 0.03$ ->4	99.0	0.2
Amoxicillin/Clavulanate	$\leq 2$	$\leq 2$	$\leq 2$ -8	99.6	0.1
Ceftriaxone	$\leq 0.25$	1	$\leq 0.25$ -8	98.6	0.5
Clindamycin	$\leq 0.25$	>2	$\leq 0.25$ ->2	75.3	23.7
Erythromycin	$\leq 0.25$	>8	$\leq 0.25$ ->8	52.2	46.6
<b>penicillin-resistant (2,117)</b>					
Garenoxacin	0.06	0.06	$\leq 0.03$ ->4	>99.9 <sup>a</sup>	<0.1 <sup>a</sup>
Ciprofloxacin	1	2	$\leq 0.25$ -4	-	-
Levofloxacin	1	1	0.06->4	98.1	1.8
Gatifloxacin	0.25	0.5	0.06->4	98.3	1.5
Amoxicillin/Clavulanate	$\leq 2$	8	$\leq 2$ ->8	36.2	11.1
Ceftriaxone	1	2	$\leq 0.25$ -16	78.8	5.0
Clindamycin	$\leq 0.25$	>8	$\leq 0.25$ ->8	65.4	33.4
Erythromycin	4	>8	$\leq 0.25$ ->8	29.2	70.2
<b><i>H. influenzae</i></b>					
<b><math>\beta</math>-lactamase-negative (8,395)</b>					
Garenoxacin	$\leq 0.03$	$\leq 0.03$	$\leq 0.03$ ->4	>99.9 <sup>a</sup>	<0.1 <sup>a</sup>
Ciprofloxacin	$\leq 0.03$	$\leq 0.03$	$\leq 0.03$ ->2	>99.9	<0.1
Levofloxacin	$\leq 0.03$	$\leq 0.03$	$\leq 0.03$ -2	100.0	0.0
Gatifloxacin	$\leq 0.03$	$\leq 0.03$	$\leq 0.03$ -4	>99.9	<0.1

Organism/antimicrobial agent (no. tested)	MIC ( $\mu\text{g/ml}$ )			Category:	
	50%	90%	Range	% susceptible	% resistant
<b><i>H. influenzae</i></b>					
<b><math>\beta</math>-lactamase-producers (2,374)</b>					
Garenoxacin	$\leq 0.03$	$\leq 0.03$	$\leq 0.03$ -0.12	100.0 <sup>a</sup>	0.0 <sup>a</sup>
Ciprofloxacin	$\leq 0.03$	$\leq 0.03$	$\leq 0.03$ -0.5	100.0	0.0
Levofloxacin	$\leq 0.03$	$\leq 0.03$	$\leq 0.03$ -0.25	100.0	0.0
Gatifloxacin	$\leq 0.03$	$\leq 0.03$	$\leq 0.03$ -0.12	100.0	0.0
<b><i>M. catarrhalis</i> (4,601)</b>					
Garenoxacin	$\leq 0.03$	$\leq 0.03$	$\leq 0.03$ -0.5	100.0 <sup>a</sup>	0.0 <sup>a</sup>
Ciprofloxacin	$\leq 0.03$	0.06	$\leq 0.03$ -1	100.0	0.0
Levofloxacin	$\leq 0.03$	0.06	$\leq 0.03$ -1	100.0	0.0
Gatifloxacin	$\leq 0.03$	$\leq 0.03$	$\leq 0.03$ -0.5	100.0	0.0

a. A susceptible breakpoint of  $\leq 2 \mu\text{g/ml}$  and a resistant breakpoint of  $\geq 8 \mu\text{g/ml}$  were used for comparative purposes only.  
b. - = No breakpoint has been established by the NCCLS.

**Table 2.** In vitro activity of garenoxacin against *S. pneumoniae* according to geographic region (SENTRY Program, 1999-2002).

Geographic region/antimicrobial agent (no. tested)	MIC ( $\mu\text{g/ml}$ )		Category:	
	50%	90%	% susceptible	% resistant
<b>North America (6,305)</b>				
Garenoxacin	0.06	0.06	>99.9 <sup>a</sup>	<0.1 <sup>a</sup>
Ciprofloxacin	1	2	- <sup>b</sup>	-
Levofloxacin	1	1	99.0	0.9
Gatifloxacin	0.25	0.5	98.7	0.8
Penicillin	$\leq 0.03$	2	69.3	16.1
Erythromycin	$\leq 0.25$	8	75.5	23.7
<b>Europe (3,382)</b>				
Garenoxacin	0.06	0.06	99.9 <sup>a</sup>	0.1 <sup>a</sup>
Ciprofloxacin	1	2	-	-
Levofloxacin	1	1	99.4	0.5
Gatifloxacin	0.25	0.5	99.4	0.5
Penicillin	$\leq 0.03$	2	69.3	16.0
Erythromycin	$\leq 0.25$	>8	72.2	26.9
<b>Latin America (1,416)</b>				
Garenoxacin	0.06	0.06	100.0 <sup>a</sup>	0.0 <sup>a</sup>
Ciprofloxacin	1	2	-	-
Levofloxacin	1	1	99.8	0.2
Gatifloxacin	0.25	0.5	99.7	0.3
Penicillin	$\leq 0.03$	2	72.5	12.8
Erythromycin	$\leq 0.25$	2	87.0	12.2
<b>Asia-Pacific-South Africa (1,368)</b>				
Garenoxacin	0.06	0.06	100.0 <sup>a</sup>	0.0 <sup>a</sup>
Ciprofloxacin	1	2	-	-
Levofloxacin	1	1	98.2	1.6
Gatifloxacin	0.25	0.5	98.5	1.3
Penicillin	0.03	4	56.1	28.3
Erythromycin	$\leq 0.25$	>8	52.9	47.0

a. A susceptible breakpoint of  $\leq 2 \mu\text{g/ml}$  and a resistant breakpoint of  $\geq 8 \mu\text{g/ml}$  were used for comparative purposes only.  
b. - = No breakpoint has been established by the NCCLS.

**Table 3.** Antimicrobial activity of garenoxacin and comparators against *S. pneumoniae* stratified by the year of isolation.

Year/antimicrobial agent (no. tested)	MIC ( $\mu\text{g/ml}$ )		Category:	
	50%	90%	% susceptible	% resistant
<b>1999 (2,818)</b>				
Garenoxacin	0.06	0.06	100.0 <sup>a</sup>	0.0 <sup>a</sup>
Ciprofloxacin	1	2	- <sup>b</sup>	-
Levofloxacin	1	1	99.2	0.7
Gatifloxacin	0.25	0.5	99.3	0.5
Penicillin	$\leq 0.03$	2	68.0	14.4
Erythromycin	$\leq 0.25$	8	76.9	22.5

## RESULTS

Year/antimicrobial agent (no. tested)	MIC ( $\mu\text{g/ml}$ )		Category:	
	50%	90%	% susceptible	% resistant
<b>2000 (3,232)</b>				
Garenoxacin	0.06	0.06	>99.9 <sup>a</sup>	<0.1 <sup>a</sup>
Ciprofloxacin	1	2	-	-
Levofloxacin	1	1	99.2	0.8
Gatifloxacin	0.25	0.5	99.2	0.7
Penicillin	$\leq 0.03$	2	66.0	18.5
Erythromycin	$\leq 0.25$	>8	71.8	27.6
<b>2001 (3,446)</b>				
Garenoxacin	0.06	0.06	>99.9 <sup>a</sup>	<0.1 <sup>a</sup>
Ciprofloxacin	1	2	-	-
Levofloxacin	1	1	99.2	0.7
Gatifloxacin	0.25	0.5	99.3	0.7
Penicillin	$\leq 0.03$	2	67.2	20.0
Erythromycin	$\leq 0.25$	>8	70.5	28.9
<b>2002 (2,975)</b>				
Garenoxacin	0.06	0.06	>99.9 <sup>a</sup>	<0.1 <sup>a</sup>
Ciprofloxacin	1	2	-	-
Levofloxacin	1	1	99.0	0.9
Gatifloxacin	0.25	0.5	99.0	0.8
Penicillin	$\leq 0.03$	2	72.1	14.3
Erythromycin	$\leq 0.25$	>8	75.4	23.5

a. A susceptible breakpoint of  $\leq 2 \mu\text{g/ml}$  and a resistant breakpoint of  $\geq 8 \mu\text{g/ml}$  were used for comparative purposes only.  
b. - = No breakpoint has been established by the NCCLS.

## CONCLUSIONS

- Garenoxacin was the most active quinolone tested against a large worldwide collection of *S. pneumoniae* (12,461 strains; MIC<sub>90</sub>, 0.06  $\mu\text{g/ml}$ ).
- Garenoxacin showed similar potency and spectrum to the other quinolones against the most frequently Gram-negative species isolated from community-acquired respiratory tract infections.
- Comprehensive multicenter surveillance programs such as the SENTRY Program remain important to continually monitor the comparative activity of older and investigational antimicrobial agents.

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