

# Activity of CEM-101 Compared to Other Agents Against Macrolide Susceptible and-Resistant Streptococci

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## Background:

Strains of *S. pneumoniae* resistant to  $\beta$ -lactams, macrolides, quinolones and other agents occur worldwide and resistant non-vaccine serotypes have appeared. CEM-101 is member of the macrolide-ketolide group which is 2-4 times more active than telithromycin against macrolide resistant pneumococci. Infections caused by drug-resistant group A streptococci are encountered worldwide and sometimes life-threatening infections caused by these organisms are encountered. *Streptococcus pyogenes* strains, although retaining their  $\beta$ -lactam susceptibility are sometimes macrolide resistant. Telithromycin is active against all macrolide resistant *S. pyogenes* genotypes except for *erm(B)*. We tested 1) activity of CEM-101 compared to those of erythromycin, azithromycin, clarithromycin, telithromycin, clindamycin, penicillin G, amoxicillin/clavulanate, levofloxacin and moxifloxacin against 124 *S. pyogenes* strains.

## Methods:

The 221 pneumococcal clinical isolates included 50 macrolide susceptible and 171 macrolide resistant strains. Of these 53 were penicillin G susceptible, 63 intermediate and 105 penicillin resistant by old CLSI breakpoints; 27 strains were quinolone resistant with defined QRDR mutations. Macrolide resistant strains comprised 54 with *erm(B)*, 51 *mef(A)*, 4 *erm(A)*, 31 *erm(B) + mef(A)*, 27 with L4, and 4 with 23S rRNA ribosomal protein mutations. The group A streptococci comprised 26 macrolide susceptible and 98 macrolide resistant organisms [19 *erm(B)*, 38 *mef(A)*, 40 *erm(A)*, 1 strain with L4 ribosomal protein mutation]. Agar dilution with Mueller-Hinton agar + 5% sheep blood with inocula  $10^4$  cfu/spot was used. Plates were incubated overnight in air for 35°C with usual quality controls.

## Results:

Pneumococcal MIC<sub>50</sub> and MIC<sub>90</sub> values ( $\mu$ g/ml) were as follows:

Drug	Macrolide susceptible (50)			Macrolide resistant (172)		
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	MIC <sub>50</sub>	MIC <sub>90</sub>
CEM-101	0.002-0.015	0.008	0.015	0.004-1	0.06	0.25
Erythro	0.03-0.25	0.06	0.125	1->64	>64	>64
Azithro	0.06-0.25	0.125	0.125	1->64	>64	>64
Clarithro	0.015-0.06	0.03	0.06	0.25->64	32	>64
Telithro	0.015-0.03	0.03	0.03	0.03-2	0.125	0.5
Clinda	0.015-0.06	0.03	0.06	0.03->64	0.125	>64
Amox/clav	0.015-8	0.5	2	0.015-16	1	8
Pen G	0.015-8	1	2	0.008->16	1	4
Levo	1-32	1	16	0.06-32	1	2
Moxi	0.125-8	0.25	4	0.125-4	0.25	0.5

MICs for group A streptococci were as follows:

Drug	Macrolide susceptible (26)			Macrolide resistant (98)		
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	MIC <sub>50</sub>	MIC <sub>90</sub>
CEM-101	0.008-0.03	0.015	0.03	0.015-1	0.06	0.5
Erythro	0.03-0.25	0.06	0.125	2->64	16	>64
Azithro	0.06-0.25	0.125	0.25	0.5->64	8	>64
Clarithro	0.015-0.06	0.03	0.06	0.25->64	4	>64
Telithro	0.03-0.06	0.06	0.06	0.03-16	0.25	8
Clinda	0.03-0.125	0.06	0.06	0.03->64	0.125	>64
Amox/clav	0.015-0.03	0.03	0.03	<0.015-0.125	0.03	0.03
Pen G	<0.008-0.125	0.015	0.015	<0.008-0.125	0.015	0.015
Levo	0.5-1	0.5	0.5	0.5-2	0.5	1
Moxi	0.125-0.25	0.25	0.25	0.125-0.5	0.25	0.25

CEM-101 had an MIC range against macrolide susceptible pneumococci of 0.002-0.015 µg/ml and a range against macrolide resistant pneumococci (all phenotypes) of 0.004-1 µg/ml. Only 3 strains with *erm(B)* [with and without *mef(A)*] had CEM-101s MIC of 1.0 µg/ml and 218/221 strains had CEM-101 MICs of ≤ 0.5 µg/ml. By contrast corresponding telithromycin MIC ranges were 0.015-0.03 µg/ml for macrolide susceptible and 0.03-2 µg/ml for macrolide resistant strains, respectively. CEM-101 MICs were up to four fold lower than those of telithromycin against macrolide susceptible and resistant strains. MICs of erythromycin, azithromycin, clarithromycin were highest in *erm(B)* [with and without *mef(A)*], L4 and 23S rRNA strains and clindamycin resistance only seen amongst strains containing *erm(B)* with or without *mef(A)*. All strains were β-lactam and quinolone susceptible. Against group A streptococci, CEM-101 MICs ranged between 0.008-0.03 µg/ml against macrolide susceptible, and between 0.015-1 µg/ml against macrolide resistant strains. Against *erm(B)* strains, erythromycin, azithromycin, clarithromycin MICs were 32- > 64 µg/ml while 17/19 strains had telithromycin MICs between 4 and 16 µg/ml; comparative CEM-101 MICs were 0.015-1 µg/ml. By comparison, *erm(A)* and *mef(A)* strains had CEM-101 MICs of 0.015-0.5 µg/ml, clindamycin and telithromycin MICs ≤ 1 µg/ml, with erythromycin, azithromycin and clarithromycin MICs of 0.5- > 64 µg/ml.

## Conclusions:

CEM-101 had the lowest MICs of all macrolides and ketolides against all pneumococcal strains including macrolide resistant phenotypes. CEM-101 was very potent against all strains of group A streptococci tested irrespective of macrolide resistance phenotype.