

# Retapamulin (SB-275833), A Novel Topical Pleuromutilin, Is Active Against Community Associated Methicillin- and Mupirocin-Resistant *S. aureus* Isolates From Uncomplicated Skin And Skin Structure Infections (SSSIs)

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## Revised Abstract

**Background:** Retapamulin (SB-275833) is a novel pleuromutilin currently in development as a topical antimicrobial for treatment of skin and skin structure infections (SSSIs). Retapamulin has a unique mode of action and shows no target specific cross-resistance to other classes of antibiotics. Retapamulin is highly active against bacterial isolates carrying resistance determinants to established agents. **Methods:** Clinical isolates of *Staphylococcus aureus*, from skin infections were collected from 53 sites in 13 countries during 2004–2005. All isolates were sent to a central laboratory for testing and confirmation of identification and methicillin resistance. Organisms were frozen at -70°C prior to evaluation. Susceptibility testing was performed using broth microdilution panels. A total of 14 antimicrobials were compared with retapamulin in this study. Quality controls were performed each day of testing. All testing followed Clinical and Laboratory Standards Institute (CLSI, formerly the National Committee for Clinical Laboratory Standards [NCCLS]) guidelines. **Results:** Methicillin resistance (MRSA) was detected in 649/1975 (32.9%) of *S. aureus* isolates examined. Mupirocin resistance (MUP-R) was detected in 99/649 (15.3%) of MRSAs, and in 95/1326 (7.2%) of methicillin-susceptible SA (MSSA). Retapamulin MIC<sub>90</sub> values against the MRSA/MRSA+MUP-R isolates were 0.12/0.12 µg/mL. The same sets of isolates exhibited MIC<sub>50</sub>s (expressed as µg/mL) of 16/>256, MUP; 32/64, gentamicin; 64/>64, neomycin; 2/2, fusidic acid; >128/>128, bacitracin; >32/>32, clindamycin; >32/>32, erythromycin; >32/>32, tetracycline; 2/2, linezolid; 64/256, cephalothin; and 32/>32, amoxicillin/clavulanic acid, respectively. **Conclusion:** Retapamulin demonstrates excellent *in vitro* activity against skin bacterial isolates resistant to established agents including β-lactams and mupirocin. This activity confers an advantage for retapamulin over current topical and oral antimicrobial agents commonly used in the treatment of uncomplicated SSSIs.

## Introduction

Retapamulin (SB-275833; Figure 1), a novel derivative of the pleuromutilin class of antimicrobials, is currently in development for the topical treatment of a variety of Gram positive pathogens associated with secondarily infected traumatic lesions and dermatoses. The pleuromutilins are potent inhibitors of protein synthesis in bacteria through the interference of peptide bond formation by binding to the peptidyl transferase center of the 50S ribosomal subunit.<sup>1</sup> Due to the unique pleuromutilin mode of action, retapamulin shows no target specific cross-resistance to other classes of antibacterials.

Mupirocin is a topical antimicrobial commonly used in the treatment of uncomplicated skin infections and also nasal decolonization of methicillin-resistant *Staphylococcus aureus* (MRSA). Mupirocin activity against MRSA has decreased since the advent of mupirocin-resistant *S. aureus* and is linked to increased usage and exposure to the drug.<sup>2,3</sup> Therefore, there is an increased need for new antibiotics with activity against drug-resistant organisms due to a rise in drug resistance and the potential for reduced effectiveness of existing treatments. This study looked at the *in vitro* activity of retapamulin against a geographically diverse population of MRSA and mupirocin-resistant *S. aureus* from skin and skin structure infections (SSSI).

## Materials and Methods

- MIC endpoints were determined by broth microdilution and interpreted according to Clinical and Laboratory Standards Institute (CLSI, formerly the National Committee for Clinical Laboratory Standards [NCCLS]) guidelines<sup>4</sup> for retapamulin and 14 comparators in dried broth microdilution panels (Trek Diagnostic Systems Ltd, West Sussex, UK). Comparator antimicrobial agents included: amoxicillin-clavulanic acid, bacitracin, ceftriaxone, cephalothin, clindamycin, cloxacillin, erythromycin, fusidic acid, gentamicin, linezolid, mupirocin, neomycin, penicillin, and tetracycline.
- All study organisms were clinical isolates collected and frozen at -70°C from March 2004 to March 2005 from 53 sites in 13 countries: Australia, Belgium, Canada, France, Germany, India, Italy, Mexico, Singapore, South Africa, Spain, the UK and the USA. All isolates were obtained from SSSI, primarily from infections seen in community settings. Isolates were obtained from both adult and pediatric patients with one isolate per patient.
- Organism collection, transport, confirmation of organism identification, antimicrobial susceptibility testing, as well as construction and management of a centralized database, were coordinated by International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA).
- A total of 1975 *S. aureus* isolates were collected from patients in hospital and community settings and tested. Of these, 649 (32.9%) were methicillin-resistant, 194 (9.8%) were mupirocin-resistant and 99 (5.0%) were methicillin- and mupirocin-resistant. 1132 *S. aureus* isolates were from patients in the community setting. Of these, 371 (32.8%) were MRSA, 101 (8.9%) were mupirocin-resistant and 45 (4.0%) were methicillin- and mupirocin-resistant.
- Mueller-Hinton broth (Sensititre®, Cleveland, OH, USA) was used for all *Staphylococcus* species.
- The trays were incubated at 35°C in ambient air for 16–20 h before reading the MIC endpoints.
- Quality control testing was performed each day of testing as specified by the CLSI using the following isolates: *S. aureus* ATCC 29213 and *S. aureus* ATCC 25923. In addition, quality control ranges previously determined for retapamulin were used as a control.<sup>5</sup>
- The total number of isolates, MIC<sub>50</sub> (µg/mL), MIC<sub>90</sub> (µg/mL) and MIC ranges were determined for all antimicrobial agents tested. Interpretive criteria and resistant phenotypes to the corresponding antimicrobial agent were defined according to CLSI breakpoints or the literature (mupirocin and fusidic acid only). Methicillin-resistance was based upon oxacillin screening agar.

## Results

- The activity of retapamulin and comparator antimicrobials are presented in Tables 1–2 and Figures 2–4.

Table 1. MIC (µg/mL) Summary for Retapamulin Activity Against 1132 *S. aureus* Isolates Recovered from SSSIs in a Community Setting

Phenotype <sup>a,b</sup> (n)	MIC (µg/mL)		
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range
All <i>S. aureus</i> (1132)	0.06	0.12	0.004–0.5
Methicillin-susceptible (761)	0.06	0.12	0.015–0.5
Methicillin-resistant (371)	0.06	0.12	0.004–0.5
Mupirocin-susceptible (1031)	0.06	0.12	0.004–0.5
Mupirocin-resistant (101)	0.06	0.12	0.03–0.5
Mupirocin-resistant and methicillin-susceptible (56)	0.06	0.12	0.03–0.5
Mupirocin-resistant and methicillin-resistant (45)	0.06	0.12	0.03–0.25

<sup>a</sup>Phenotypes were determined by the *in vitro* susceptibility of the respective antimicrobial agent against the corresponding organism as defined in CLSI document M100-S15 unless otherwise noted; <sup>b</sup>methicillin = oxacillin activity. <sup>c</sup>Mupirocin susceptibility breakpoints (≤4 µg/mL susceptible; ≥8 µg/mL resistant) as defined by Finlay et al.<sup>7</sup>

Table 2. MIC (µg/mL) Summary for Retapamulin and Comparators Against *S. aureus* Isolates Recovered from Community Settings by Resistant Phenotype

Compound <sup>c</sup>	MRSA <sup>a</sup> (n = 371)		Mupirocin-resistant <sup>b</sup> <i>S. aureus</i> (n = 101)		Mupirocin <sup>b</sup> - and methicillin-resistant <sup>a</sup> <i>S. aureus</i> (n = 45)	
	%Res	MIC <sub>90</sub>	%Res	MIC <sub>90</sub>	%Res	MIC <sub>90</sub>
Retapamulin	NA	0.12	NA	0.12	NA	0.12
Amox-Clav <sup>d</sup>	100	16	51.5	16	100	>32
Bacitracin	NA	>128	NA	>128	NA	>128
Ceftriaxone	100	>64	48.5	>64	100	>64
Cephalothin	100	32	51.5	32	100	256
Clindamycin	39.4	>32	46.5	>32	57.8	>32
Cloxacillin	NA	16	NA	32	NA	>32
Erythromycin	87.9	>32	77.2	>32	86.7	>32
Fusidic acid	5.4	1	5.9	2	4.4	2
Gentamicin	10.5	16	10.9	16	6.7	8
Linezolid	0	2	0	2	0	2
Methicillin	100	NA	44.6	NA	100	NA
Mupirocin	12.1	8	100	>256	100	>256
Neomycin	NA	>64	NA	64	NA	>64
Penicillin	100	32	98.0	32	100	>32
Tetracycline	22.6	>32	27.7	32	20.0	32

<sup>a</sup>Phenotype was determined by the susceptibility of *S. aureus* to oxacillin as defined in the CLSI document M100-S15.<sup>6</sup> <sup>b</sup>Phenotype was determined by the susceptibility of *S. aureus* to mupirocin as defined by Finlay et al.<sup>7</sup> <sup>c</sup>Interpretive criteria of compounds defined in the CLSI document M100-S15 where available; mupirocin susceptibility (≤4 µg/mL susceptible; ≥8 µg/mL resistant) defined in Finlay et al.;<sup>7</sup> fusidic acid susceptibility (≤1 µg/mL susceptible; ≥4 µg/mL resistant) defined in Toma and Barriault;<sup>8</sup> Note: β-lactams reported as resistant for MRSA in accordance with current CLSI guidelines. <sup>d</sup>Amoxicillin/clavulanic acid was tested in a 2:1 ratio; MICs are reported based on the amoxicillin concentration. Res, resistant; NA, not available.

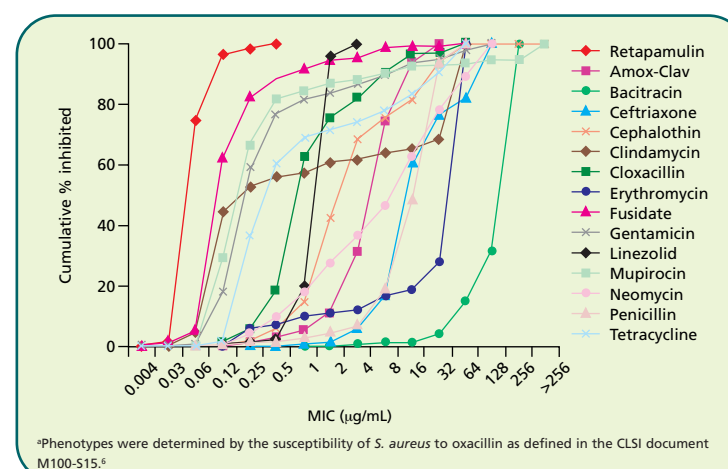


Figure 2. Cumulative Inhibition (%) at Each MIC (µg/mL) for Retapamulin and Comparators against 371 Methicillin-resistant *S. aureus* Isolates Recovered from a Community Setting

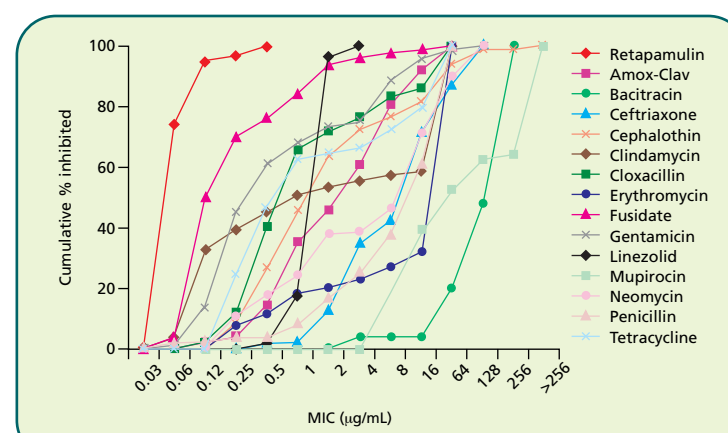


Figure 3. Cumulative Inhibition (%) at Each MIC (µg/mL) for Retapamulin and Comparators against 101 Mupirocin-resistant *S. aureus* Isolates Recovered from a Community Setting

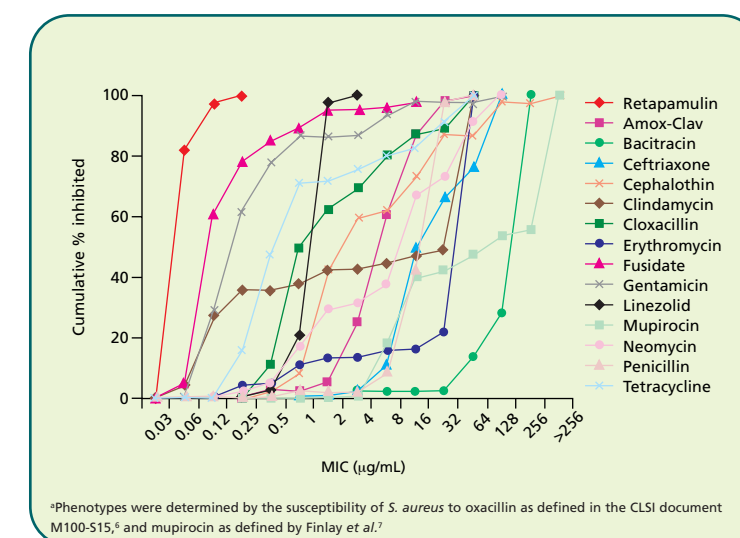


Figure 4. Cumulative Inhibition (%) at Each MIC (µg/mL) for Retapamulin and Comparators against 45 Mupirocin-resistant/Methicillin-resistant *S. aureus* Isolates Recovered from a Community Setting

## Conclusions

- Retapamulin demonstrated excellent *in vitro* activity against methicillin-resistant, mupirocin-resistant, and mupirocin-resistant/methicillin-resistant *S. aureus* isolates from uncomplicated SSSIs, with MIC<sub>90</sub> values at least 16-fold lower than those of any comparator in this study.
- Against all 1975 *S. aureus* isolates tested, retapamulin was the most potent agent *in vitro* and inhibited all isolates at a MIC of ≤0.5 µg/mL.
- Retapamulin inhibited 100% of methicillin-resistant, mupirocin-resistant, and mupirocin-resistant/methicillin-resistant *S. aureus* at concentrations of ≤0.5 µg/mL.
- Retapamulin's retention of potent *in vitro* activity against *S. aureus* strains resistant to one or more of the agents commonly used in the treatment of SSSIs could potentially provide a useful option for treatment of such infections. Further clinical trial data are required in order to assess its efficacy in patients.

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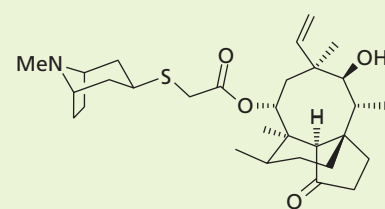


Figure 1. Chemical Structure of Retapamulin