

# New antimicrobial agents for methicillin-resistant *Staphylococcus aureus*

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In bacterial and fungal infections, optimal outcomes are obtained through the timely provision of adequate antimicrobial coverage in an initial anti-infective treatment regimen. However, selecting appropriate antimicrobial regimens to treat infections in the intensive care unit can be challenging because of the expansion of antibiotic resistance. Multidrug anti-infective regimens are typically needed to adequately cover the common important pathogens in ICUs. The term "ESKAPE" has been coined for the group that causes most hospital-acquired infections able to "escape" our antibiotic arsenal in the United States: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. Their existence mandates the discovery of new antimicrobial agents. Here, we describe novel antibacterial agents in the late stages of clinical development that show potential for treating methicillin-resistant *S. aureus* (MRSA) infections.

## Ceftaroline

Ceftaroline fosamil is a fifth-generation cephalosporin pro-drug with activity against a broad range of gram-positive and gram-negative bacteria. The active agent, ceftaroline, is active against MRSA and has a minimum inhibitory concentration for 90% of organisms (MIC<sub>90</sub>) of 1–2 µg/mL because of its enhanced binding to penicillin-binding protein 2a (PBP2a), as compared with other β-lactam antibiotics.<sup>1</sup> The drug is also active against penicillin- and cephalosporin-resistant *Streptococcus pneumoniae* and β-haemolytic streptococci, and has variable activity against *Enterococcus faecalis* but little or no activity against vancomycin-resistant *Enterococcus faecium*. Against relevant gram-negative pathogens, it has broad-spectrum activity similar to that of ceftriaxone. However, its MICs are generally higher than those of cefepime against most non-fermenting gram-negative bacteria and *Enterobacteriaceae*, and it is expected to be inactive against *Pseudomonas* spp. and *Acinetobacter* spp. Ceftaroline appears to be a weak inducer of AmpC β-lactamases, and, like other clinically available cephalosporins (besides cefepime), is labile to AmpC and expected to be clinically ineffective against AmpC isolates. Like other advanced-generation cephalosporins, ceftaroline is not reliably active against strains of *Enterobacteriaceae* that produce extended spectrum β-lactamases (ESBLs).

## ABSTRACT

In bacterial and fungal infections, optimal outcomes are obtained through the timely provision of adequate antimicrobial coverage in an initial anti-infective treatment regimen. However, selecting appropriate antimicrobial regimens to treat infections in the intensive care unit is challenging because of the expansion of antibiotic resistance. Multidrug anti-infective regimens are typically needed to adequately cover common important pathogens in ICUs.

Here, we describe novel antibacterial agents in the late stages of clinical development that show potential for treating methicillin-resistant *Staphylococcus aureus* (MRSA) infections.

These include the fifth-generation cephalosporins, ceftaroline and ceftobiprole; the glycopeptides, dalbavancin, oritavancin, and telavancin; and iclaprim.

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Early-phase clinical trials established a dosing regimen for ceftaroline of 600 mg intravenously (IV) every 12 hours (as a 1-hour infusion) as the preferred regimen for future study. Less than 20% of the drug is protein bound in serum, and it has a volume of distribution similar to the extracellular fluid volume at around 16–17 L. Ceftaroline is primarily eliminated by renal excretion, and multiple-dose pharmacokinetic studies have shown the half-life is around 2.5–3 hours. It does exhibit an extended half-life or area under the plasma concentration time curve under conditions of mild-to-moderate renal impairment, and would be expected to require dose adjustment in these populations. No data are currently available on ceftaroline clearance in dialysis. Its potential for use in pneumonia is supported by the finding that lung tissue penetration in rabbits at the end of ceftaroline infusion was 42% of serum concentrations.<sup>2</sup>

A phase II clinical trial has compared ceftaroline (preferred regimen for 7–14 days) with vancomycin (1 g IV every 12 hours, with or without aztreonam (1 g IV every 8 hours) for the treatment of complicated skin and skin structure infection (cSSSI).<sup>3</sup> Clinical cure rates were similar for the ceftaroline (96.7%) and standard therapy (88.9%) groups. Phase III clinical trials for this indication are now complete, but data

had not been published at the time of writing. Perhaps more interesting for ICU practitioners, phase III trials are currently ongoing to compare 5–7 days of ceftaroline therapy with ceftriaxone (1 g IV daily) for treatment of community-acquired pneumonia.

### Ceftobiprole

Ceftobiprole medocaril is another fifth-generation cephalosporin pro-drug, with a broad spectrum of activity similar to that of ceftaroline. Like ceftaroline, ceftobiprole was designed to maximise binding to PBP2a and yield potent anti-MRSA activity, with an MIC<sub>90</sub> of 2 µg/mL.<sup>4</sup> Ceftobiprole is active against cephalosporin-resistant *S. pneumoniae* and ampicillin-susceptible *E. faecalis*, but not *E. faecium*. Ceftobiprole has broader gram-negative activity than ceftaroline; it appears to have a gram-negative spectrum of activity intermediate between that of ceftriaxone and cefepime, largely because of its greater stability to AmpC β-lactamases than ceftriaxone and ceftaroline. Ceftobiprole also has activity against *P. aeruginosa*, and MICs against this pathogen are generally similar to those of cefepime and ceftazidime. Activity against *Acinetobacter* spp. appears to be highly variable. As with other advanced-generation cephalosporins, ceftobiprole is not reliably active against ESBL-producing bacteria.

The volume of distribution is similar to the extracellular fluid volume, at about 18 L, although this may be doubled in patients with ventilator-associated pneumonia. There are currently no data on the epithelial lining fluid penetration of ceftobiprole, but a pharmacokinetic study is ongoing to evaluate concentrations of ceftobiprole in bronchoalveolar lavage fluid after IV infusion. The drug is 16% bound to plasma proteins, is primarily eliminated in the urine, and has a half-life of around 3–4 hours. Because of its extensive renal clearance, dose adjustments have been proposed for patients with mild-to-moderate renal impairment. Ceftobiprole appears to be removed effectively by some haemodialysis modalities.

Results of early phase clinical trials and Monte Carlo simulations suggested two dosing regimens for ceftobiprole: 500 mg IV as a 1-hour infusion every 12 hours for treatment of gram-positive infections, and 500 mg IV as a 2-hour infusion every 8 hours for empirical treatment of mixed gram-positive and gram-negative infections. Two phase III clinical trials of ceftobiprole for cSSSI have been completed.<sup>5,6</sup> The first trial enrolled patients with suspected gram-positive infection and utilised a ceftobiprole regimen of 500 mg every 12 hours, compared with IV vancomycin (1 g) every 12 hours for 7–14 days. Clinical cure rates were similar for the ceftobiprole (93.3%) and vancomycin (93.5%) groups. The second trial included patients with

diabetic foot and mixed bacterial cSSSI infections and compared ceftobiprole (500 mg IV every 8 hours) with vancomycin (1 g IV every 12 hours) plus ceftazidime (1 g IV every 8 hours) for 7–14 days. Clinical cure rates were also similar for the ceftobiprole (90.5%) and standard therapy (90.2%) groups. Ceftobiprole (500 mg IV every 8 hours) was also compared with a combination of ceftazidime and linezolid for treatment of nosocomial pneumonia.<sup>7</sup> Although the study showed ceftobiprole was non-inferior versus the combination regimen, it was unexpectedly associated with lower cure rates in patients with ventilator-associated pneumonia, particularly those younger than 45 years and those with high creatinine clearance.

### Dalbavancin

Dalbavancin is a lipoglycopeptide currently under investigation. It has a bacteriocidal mechanism of action similar to that of other glycopeptides in that it complexes with the D-alanyl-D-alanine (D-Ala-D-Ala) terminal of peptidoglycan and inhibits transglycosylation and transpeptidation.<sup>8</sup> Like teicoplanin, dalbavancin possesses a lipophilic side chain that leads to both high protein-binding and an extended half-life, which allows once-weekly dosing.

Dalbavancin is more potent than vancomycin against staphylococci, and is highly active against both methicillin-susceptible *S. aureus* (MSSA) and MRSA, with MIC<sub>90</sub> values of <0.13 mg/L and 0.25 mg/L, respectively. Dalbavancin is also active against vancomycin-intermediate *S. aureus* (VISA), although MIC<sub>90</sub> ranges are higher, at 1–2 µg/mL. It inhibits streptococci, including penicillin-resistant *S. pneumoniae*, and enterococci with the VanB or VanC phenotype, but is not active against enterococci with the VanA phenotype.

Dalbavancin is administered intravenously, and the most commonly used dose in clinical trials has been 1000 mg on Day 1, followed by 500 mg weekly thereafter. This dose achieves a maximum serum concentration of 312 µg/mL, with mean serum concentrations >35 µg/mL maintained for a 7-day dosing period. The drug has a volume of distribution of 0.11 L/kg and a half-life of 147–258 hours, supporting once-weekly dosing. Only 40% is eliminated by the kidneys, with no apparent need for dose adjustments in the setting of either moderate renal or hepatic impairment. It does not appear to interact with any of the P450 cytochromes and is not known to possess any clinically relevant drug interactions.

Clinical data for dalbavancin include phase II and III trials in both uncomplicated and complicated SSSIs, and catheter-related bloodstream infections. Dalbavancin (1000 mg IV on Day 1 followed by 500 mg IV on Day 8) was compared with linezolid (600 mg twice daily for 14 days) in a randomised,

double-blind phase III trial for treatment of cSSSI.<sup>9</sup> The overall success rates at the test-of-cure visit were similar for daptomycin and linezolid, at 88.4% and 86.8%, respectively (*P* not given). Dalbavancin was compared with  $\beta$ -lactams, clindamycin, vancomycin, and linezolid in other SSSI trials, and was shown to be at least non-inferior in each.<sup>10</sup> Another phase II study evaluated dalbavancin versus vancomycin for treatment of bloodstream infections, using the weekly dalbavancin dosing regimen described above versus vancomycin, 1 g twice daily for 7 days.<sup>11</sup> Dalbavancin had a statistically higher overall success rate than vancomycin (87% versus 50%, *P* < 0.05).

Dalbavancin provides coverage for both glycopeptide-susceptible and resistant MRSA, but coverage of vancomycin-resistant enterococci (VRE) is limited. The drug has the convenience of once-weekly dosing, which should allow simplified regimens both in hospital and at home.

### Oritavancin

Oritavancin, another investigational glycopeptide, contains novel structural modifications that allow it to dimerise and anchor itself in the bacterial membrane. These modifications also confer an enhanced spectrum of activity over traditional glycopeptide antibiotics. Oritavancin has similar in-vitro activity to vancomycin against staphylococci and is equipotent against both MSSA and MRSA. It also has activity against VISA and vancomycin-resistant *S. aureus* (VRSA), but MICs are increased to 1 mg/L and 0.5 mg/L, respectively. Oritavancin is active against enterococci, including VRE; however, MICs are significantly higher against VRE than against vancomycin-susceptible strains. The drug is also active against both penicillin-susceptible and penicillin-resistant *S. pneumoniae*.

Oritavancin has been typically administered at a dose of 1.5–3 mg/kg IV once daily, as well as at a flat dose of 200 mg daily. Despite being 90% bound to plasma proteins, it is rapidly distributed to the tissues. However, its propensity for binding to pulmonary surfactant needs to be assessed, on the basis of an effect noted in a murine pneumonia model. About 60% of the administered dose of oritavancin is retained in the liver, but there is no evidence that it undergoes hepatic metabolism. In-vitro studies of cultured macrophages show intracellular levels up to 400 times those seen in the serum, but the clinical significance of this is unknown. The drug is predominantly eliminated by the kidneys, but renal clearance is very slow because of high protein binding and extensive tissue distribution, with only 5% unchanged drug recovered at 7 days after a dose.

Clinical data for oritavancin are limited. Two phase III trials evaluating oritavancin for cSSSI have been completed. In the first study, oritavancin (1.5 mg/kg or 3 mg/kg daily)

met criteria for non-inferiority versus vancomycin plus cefalexin. Patients receiving either dose of oritavancin showed a shorter mean duration of therapy (5.3 or 5.7 days, respectively) than those in the vancomycin group (11.9 days). A second cSSSI trial of a fixed oritavancin dose of 200 mg IV daily versus vancomycin plus cefalexin found clinical cure rates of 78.6% for oritavancin and 76.2% for vancomycin plus cefalexin (95% CI for difference, –3.4% to 7.8%). Again, the average duration of therapy was shorter for oritavancin than for vancomycin plus cefalexin (5.3 v 10.9 days, *P* < 0.001). An additional study (SIMPLIFI), designed to assess novel oritavancin dosing regimens in the treatment of cSSSI, compared oritavancin as a single large dose, as a dose on Day 1 with an optional dose on Day 5, or as a dose of 200 mg once daily for 3–7 days.<sup>12</sup> The study has been completed, but results were not available at the time of writing.

Oritavancin has also showed equivalence to vancomycin or an active  $\beta$ -lactam for treatment of *S. aureus* septicaemia when administered at 5–10 mg/kg daily.<sup>13</sup> Data evaluating oritavancin for treatment of meningitis and cardiac infections exist only in animal models. In these, oritavancin successfully treated meningitis caused by *S. pneumoniae* and endocarditis caused by MRSA and VRE.

Oritavancin has been well tolerated in clinical trials, with the most predominant adverse effects being headache, nausea, vomiting, sleep disorders, and injection-site reactions. Elevated aminotransferase concentrations seen in early trials of oritavancin were not seen in either of the phase III clinical trials in patients with cSSSI.

Oritavancin is highly active against both *S. aureus* and *Enterococcus* spp., covering the most resistant strains of both. However, clinical data are very limited, and it is unclear whether future studies are planned for more critical infections. The potential for oritavancin to bind to pulmonary surfactant may significantly limit its utility for treating pulmonary infections. The very high intracellular concentration profile will also need to be carefully assessed. At the time of writing, oritavancin had not yet secured approval from the US Food and Drug Administration (FDA) because of lack of adequate efficacy and safety data.

### Telavancin

Telavancin is an investigational glycopeptide derivative of vancomycin. Like oritavancin, telavancin has the ability to anchor itself in the bacterial membrane, disrupting polymerisation and cross-linking of peptidoglycan. Telavancin also interferes with the normal function of the bacterial membrane, decreasing its ability to act as a barrier. This dual mechanism helps explain telavancin's high potency and rapid bactericidal activity.<sup>14</sup>

Telavancin is bactericidal against staphylococci, including MRSA, VISA, and VRSA, with MIC<sub>90</sub> values of 0.25–1 mg/L, 0.5–2 mg/L, and 2–4 mg/L, respectively. Telavancin, like oritavancin, is potent against both penicillin-susceptible and penicillin-resistant strains of *S. pneumoniae*. It is also active against vancomycin-susceptible strains of *E. faecium* and *E. faecalis*, but MICs are increased for vancomycin-resistant strains of both species.

The usual dose of telavancin is 7.5–10 mg/kg/day. The drug is highly protein-bound and has a volume of distribution of 0.1 L/kg. It has a half-life of 7–9 hours, is predominantly eliminated by the kidneys, and will likely require dose adjustments in patients with renal impairment.

Of the investigational glycopeptides and lipoglycopeptides, telavancin has the richest set of clinical data supporting its use. A set of two identical phase III trials, ATLAS I and ATLAS II, compared telavancin (10 mg/kg per day) with vancomycin (1 g every 12 hours) for treating cSSSI.<sup>15</sup> They found telavancin to be non-inferior to vancomycin, with a combined clinical cure rate in patients with MRSA infection of 90.6% (telavancin) versus 86.4% (vancomycin, *P*=0.06). Telavancin has also been studied in hospital-acquired pneumonia. ATTAIN 1 and ATTAIN 2 were both randomised, double-blind trials with a combined population of 1503 patients, of whom 464 had documented MRSA infection. Patients were randomly allocated to receive telavancin (10 mg/kg IV once daily) or vancomycin (1 g IV every 12 hours). Telavancin was shown to be non-inferior to vancomycin. In addition, preliminary results showed that clinical cure rates were 82% for telavancin and 74% for vancomycin in patients infected with MRSA (*P*, not significant). Also of interest was the finding that a subset of patients with ventilator-associated pneumonia had a cure rate of 80% for telavancin and 68% for vancomycin (*P* not given).

Telavancin has been well tolerated in clinical trials, with the most common adverse effects being taste disturbances, headache and dizziness. Other potentially serious adverse effects include raised serum creatinine concentration, microalbuminuria, and decreased platelet count, each of which occurred at rates similar to those for comparator agents. Of potential concern is an apparent risk of low birth weight and limb defects in pregnant animals receiving telavancin. The FDA has recommended that this drug should be used in pregnant women only when the benefits outweigh the risk.

### Iclaprim

Iclaprim (formerly AR-100 or Ro 48-2622) is an investigational IV diaminopyrimidine antibacterial agent that, like trimethoprim, selectively inhibits the dihydrofolate reductase enzyme of both gram-positive and gram-negative bac-

teria, exerting bactericidal effects.<sup>16</sup> Iclaprim is active against MSSA, community- and nosocomial-MRSA, VISA, VRSA, groups A and B streptococci, and pneumococci, and is variably active against enterococci. Iclaprim appears to have gram-negative activity similar to that of trimethoprim, including activity against *E. coli*, *K. pneumoniae*, *Enterobacter* spp., *Citrobacter freundii*, and *Proteus vulgaris*. Iclaprim also appears to have activity against the atypical respiratory pathogens *Legionella* and *Chlamydia pneumoniae*, but is not active against *P. aeruginosa* or anaerobes. Although iclaprim appeared to be rendered bacteriostatic against a wild-type isolate of *S. aureus* in the presence of increasing concentrations of thymidine in vitro, the effect of thymidine release from bacteria and infected host tissues on its activity in vivo is unknown.

Iclaprim achieves a maximum serum concentration of 0.85 µg/mL after a dose of 0.8 mg/kg by intravenous infusion over 30 minutes and appears to have linear pharmacokinetics. It is 93% plasma-protein bound, has a volume of distribution of 1.15 L/kg, and achieves concentrations in epithelial lining fluid that exceed plasma concentrations by a factor of 2.7–12.<sup>17</sup> The drug is primarily metabolised to phase I metabolites, and subsequently to glucuronide metabolites. Its half-life is 2.5–4.1 hours. Clearance is reduced in moderate hepatic insufficiency to the extent that dosage adjustments appear warranted, but is unaffected by renal insufficiency.

A drug application for iclaprim as treatment of cSSSI was submitted to the US FDA in 2008,<sup>16</sup> on the basis of combined results from two similar randomised, multicentre, double-blind phase III trials versus linezolid (ASSIST-1 and ASSIST-2).<sup>18</sup> In revised analyses by FDA reviewers, iclaprim (0.8 mg/kg every 12 hours) failed to achieve non-inferiority versus linezolid for treatment of cSSSI, and was potentially inferior to linezolid in ASSIST-1. These findings cast doubt on the feasibility of treating cSSSI with iclaprim. However, at the time of writing, a clinical trial comparing iclaprim with vancomycin for treatment of hospital-acquired, ventilator-associated or health care-associated pneumonia was recruiting.<sup>19</sup>

Overall, iclaprim appears to be fairly well tolerated, but it has been associated with gastrointestinal disturbances, including elevations in hepatic aminotransferase levels, anaemia, pyrexia, headache, and pruritis. Iclaprim also prolongs the QTc interval, but was not associated with any known cases of torsades de pointes or other ventricular arrhythmias in phase III studies. The drug may inhibit CYP3A4 and P-glycoprotein, but the clinical significance of any potential resultant drug interactions is uncertain.

The possible role of iclaprim in treating infections in the ICU is unclear. Recent FDA advisory committee deliberations suggest that it may not have a role for cSSSI. However, at

the time of writing, it was being studied for hospital-acquired, ventilator-associated or health care-associated pneumonia; pending results, it may prove useful as a component of a multidrug regimen for these infections because of its activity against MRSA. However, its inability to cover *P. aeruginosa* will likely limit its utility as empirical monotherapy for many infections in the ICU.

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**References**

- 1 Ge Y, Biek D, Talbot GH, Sahm DF. In vitro profiling of ceftaroline against a collection of recent bacterial clinical isolates from across the United States. *Antimicrob Agents Chemother* 2008; 52: 3398-407.
- 2 Jacqueline C, et al. Penetration of ceftaroline (PPI-0903), a new cephalosporin, into lung tissues: measurement of plasma and lung tissue concentrations after a short IV infusion in the rabbit. In: Abstracts of the 46th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco; 2006: abstract A-1938.
- 3 Talbot GH, Thye D, Das A, Ge Y. Phase 2 study of ceftaroline versus standard therapy in the treatment of complicated skin and skin structure infections. *Antimicrob Agents Chemother* 2007; 51: 3612-6.
- 4 Fritsche TR, Sader HS, Jones RN. Antimicrobial activity of ceftobiprole, a novel anti-methicillin-resistant *Staphylococcus aureus* cephalosporin, tested against contemporary pathogens: results from the SENTRY antimicrobial surveillance program (2005–2006). *Diagn Microbiol Infect Dis* 2008; 61: 86-95.
- 5 Noel GJ, Strauss RS, Amsler K, et al. Results of a double-blind, randomized trial of ceftobiprole treatment of complicated skin and skin structure infections caused by gram-positive bacteria. *Antimicrob Agents Chemother* 2008; 52: 37-44.
- 6 Noel GJ, Bush K, Bagchi P, et al. A randomized, double-blind trial comparing ceftobiprole medocartil with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin structure infections. *Clin Infect Dis* 2008; 46: 647-55.
- 7 Noel GJ, et al. Ceftobiprole versus ceftazidime combined with linezolid for treatment of patients with nosocomial pneumonia. In: Abstracts of the 48th Annual Interscience Conference on Antimi-

- crobial Agents and Chemotherapy. Washington, DC; 2008: abstract K-486.
- 8 Zhanel GG, Trapp S, Gin AS, et al. Dalbavancin and telavancin: novel lipoglycopeptides for the treatment of gram-positive infections. *Expert Rev Anti Infect Ther* 2008; 6: 67-81.
- 9 Jauregui LE, Babazadeh S, Seltzer E, et al. Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. *Clin Infect Dis* 2005; 41: 1407-15.
- 10 Seltzer E, Dorr MB, Goldstein BP, et al. Once-weekly dalbavancin versus standard-of-care antimicrobial regimens for treatment of skin and soft-tissue infections. *Clin Infect Dis* 2003; 37: 1298-303.
- 11 Raad I, Darouiche R, Vazquez J, et al. Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens. *Clin Infect Dis* 2005; 40: 374-80.
- 12 A study for patients with complicated skin and skin structure infections (SIMPLIFI). <http://clinicaltrials.gov/ct2/show/NCT00514527?term=oritavancin&rank=1>, (accessed Feb 2009).
- 13 Loutit JS, et al. Phase 2 trial comparing four regimens of oritavancin vs. comparator in the treatment of patients with *S aureus* bacteraemia. Abstract P541. *Clin Microbiol Infect* 2004; 10: 122.
- 14 Leonard SN, Rybak MJ. Telavancin: an antimicrobial with a multi-functional mechanism of action for the treatment of serious gram-positive infections. *Pharmacotherapy* 2008; 28: 458-68.
- 15 Dunbar LM, Tang DM, Manausa RM. A review of telavancin in the treatment of complicated skin and skin structure infections (cSSSI). *Ther Clin Risk Manag* 2008; 4: 235-44.
- 16 Food and Drug Administration. FDA briefing document for Anti-infective Drugs Advisory Committee Meeting, November 20, 2008 (Iclaprim for the treatment of complicated skin and skin structure infection). <http://fda.gov/ohrms/dockets/ac/08/briefing/2008-4394b3-01-FDA.pdf> (accessed Dec 2008).
- 17 Andrews J, Honeybourne D, Ashby J, et al. Concentrations in plasma, epithelial lining fluid, alveolar macrophages and bronchial mucosa after a single intravenous dose of 1.6 mg/kg of iclaprim (AR-100) in healthy men. *J Antimicrob Chemother* 2007; 60: 677-80.
- 18 Hadvary P, et al. Clinical efficacy of iclaprim in complicated skin and skin structure infection (cSSSI): results of combined ASSIST phase III studies. In: Abstracts of the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC; 2008: abstract L-1512.
- 19 Clinical Efficacy of Intravenous Iclaprim versus Vancomycin in the Treatment of Hospital-Acquired, Ventilator-Associated, or Health-Care-Associated Pneumonia. <http://www.clinicaltrials.gov/ct2/show/NCT00543608?term=iclaprim&rank=1> (accessed Jan 2009). □