Antimicrobial Development in the Era of Emerging Resistance

Antonio Sorlozano[a], Cristina Carrasco[a], Jose Cabeza[b], Enrique Villegas[a] and Jose Gutierrez[a,*]

[a]Department of Microbiology, School of Medicine, University of Granada, Spain; [b]Service of Pharmacy, San Cecilio University Hospital, Granada, Spain

Abstract: Antibiotics currently under study by the Food and Drugs Administration include: faropenem (for treatment of sinusitis, bronchitis, and community-acquired pneumonia), dalbavancin (for catheter infections), telavancin (for treatment of nosocomial pneumonia), oritavancin (for bacteremia), ceftobiprole and iclaprim (for pneumonias). Moreover, all of them would be useful for skin and soft tissue infections.

Key Words: Faropenem, dalbavancin, telavancin, oritavancin, ceftobiprole, iclaprim.

INTRODUCTION

Resistance among pathogens commonly responsible for both nosocomial and community acquired infections is increasing at an alarming rate. Infections due to these resistant organisms are associated with greater costs, higher morbidity, and higher mortality than infections due to similar nonresistant organisms [1]. The past few years have seen a major rise in resistance to antibiotics among Gram-negative bacteria (beta-lactamase [ESBL]-producing enterobacteria, carbapenem-resistant *P. aeruginosa* and *A. baumannii* …) [2] and, especially, among Gram-positive bacteria (methicillin-resistant *S. aureus* [MRSA], glycopeptide-intermediate [GISA] or resistant *S. aureus* [GRSA], vancomycin-resistant enterococci [VRE], multi-drug resistant *S. pneumoniae* [MDRSP]) [3]. This trend has considerably reduced therapeutic options and brought about a need for novel antibiotics.

Antibiotics currently under study by the Food and Drugs Administration (FDA) for skin and soft tissue infections caused by Gram-positive (including MRSA) and, in some cases, Gram-negative bacteria include: dalbavancin (for catheter infections- phase II), telavancin (for nosocomial pneumonia- in phase III trial), oritavancin (for bacteremia-phase II), ceftobiprole (for pneumonias- phase III) and iclaprim (for pneumonias- phase II). Faropenem may be applied in the future to treat mild respiratory infections (sinusitis, bronchitis, and community-acquired pneumonia).

The objective of our study will be to review the *in vitro* antibiotic activity, action mechanisms, and resistance (if reported) of the above antibiotics.

FAROPENEM

Structure

Faropenem (SY5555) or 4-thia-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid, 6-(1-hydroxyethyl) 7-oxo-3-(tetrahydro-2-furanyl)-, monosodium salt (Fig. **1**) is a new oral penem antimicrobial agent, which has an unsaturated thia-
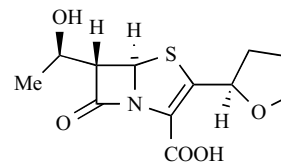

Fig. (1). Structure of faropenem.

zole ring and is a structural hybrid between the penicillin and carbapenem nucleus [4-6]. At present, faropenem is the only representative of this subclass that is either in its preregistration phase (as faropenem medoxomil in USA) or is commercially available (as faropenem sodium in Japan) [7, 8].

Thus, faropenem as a representative of the penem subclass is chemically distinct from the carbapenems. The introduction of a C-2 side chain (which is a chiral, a basic tetrahydroforuran ring) to the penem skeleton led to the development of faropenem, with unique characteristics distinct from carbapenems and other beta-lactam drugs [9]. The stability and neutral C-2 side chain of faropenem versus the instability of carbapenems and positively charged side chain at physiological pH have clinical relevance in that. First, carbapenems as injectable drugs have a limited dosing flexibility. Second, excitability of the central nervous system is closely correlated to the positive charge of the molecule. Third, the protonation state (and thus charge) of the C-2 side chain has an impact on the antibacterial spectrum of the penems [4].

The subclass of carbapenems covers hospital pathogens, whereas the penem subclass representative faropenem is active against pathogens causing community-acquired infections. In this context it is worth noting that all the carbapenems have to be administered parenterally; however, faropenem medoxomil has very good oral bioavailability. Therefore, faropenem medoxomil may be a suitable candidate for sequential therapy and a step-down therapy following previous intravenous treatment of infections like community-acquired pneumonia with e.g., ertapenem [4].

Mechanism of Action

Faropenem, like the other β-lactam antibiotics, acts by blocking cell wall synthesis through binding to PBPs. It

*Address correspondence to this author at the Department of Microbiology, School of Medicine, Avda de Madrid 11, E-18012 Granada, Spain; E-mail: E-mail: josegf@ugr.es

shows greater affinity for those of high molecular weight. Thus, for example, it shows greater affinity for PBP1, followed by PBP3 and PBP2 of *S. aureus* and *S. pneumoniae*; greater affinity for *E. coli* PBP2 than for *E. coli* PBP1A, PBP1B, PBP3 and PBP4, as well as a greater affinity for *P. vulgaris* PBP4 and for *S. marcescens* PBP2 and PBP4 [10].

Spectrum of Activity

Faropenem is active against *Staphylococcus* spp., with the exception of MRSA isolates; against *S. pneumoniae* (including MDRSP isolates), *S. milleri*, *S. viridans* (except penicillin-resistant isolates) and other β-haemolytic streptococci of the A and B groups, and against *Neisseria* spp. [11-15]. However, it is not active against *Enterococcus* spp. [15, 16].

Activity against Gram-negative bacteria is less marked, perhaps due to the absence of charge in the position 2 substitute [17, 18]. Even so, faropenem has shown good activity against some species of *Enterobacteriaceae* (including ESBLs or AmpC-producing isolates) [19], as well as against *H. pylori* [7] and two of the most common respiratory pathogens, i.e. *H. influenzae* and *M. catarrhalis* (including β-lactamase-producing isolates) [20-23]. However, bacteria such as *Enterobacter* spp., *Proteus* spp., *Providencia* spp., *Serratia* spp. or *Morganella* spp. show reduced susceptibility against this antibiotic [13]. Additionally, faropenem is not active against *P. aeruginosa* or *S. maltophilia*, amongst other non-fermenting Gram-negative bacilli [13, 15, 16, 24].

Faropenem is equally active against some anaerobic bacteria such as *C. perfrigens*, *B. subtilis*, *B. forsythus*, *B. ureolyticus*, *Prevotella* spp., *F. nucleatum* and *P. gingivalis*, including β-lactamase-producing isolates [25].

Table **1** shows the *in vitro* activity of faropenem against different bacteria of clinical interest.

Resistance

Like the other β-lactam agents, the bacterial mechanisms of resistance against faropenem include inactivation through carbapenemases, alteration of PBPs, reduction of permeability of the external membrane and active efflux.

Faropenem is highly stable against the majority of β-lactamases, including ESBLs and AmpC [4, 15, 16, 24, 26]. Said stability may be derived from the presence of the 1-(R)-hydroxyethyl group in the C6 position of the bycyclic molecule [4, 9]. Some β-lactamases of the A-class, such as Imi-I from *E. cloacae*, maintain a certain hydrolytic capacity against carbapenems and penems; notwithstanding, the only β-lactamases really active against this antibiotic are metallo-β-lactamases [4, 16].

The intrinsic resistance of *P. aeruginosa* to faropenem entails at least three mechanisms: multidrug active expulsion systems, mainly the MexAB-OprM system, the inability to enter through the OprD porine and the low binding affinity of the penem to surface PBPs. The absence of expression of just one of those mechanisms in the bacteria would be enough to improve the activity of faropenem against this pathogen. This is the reason why the application of membrane permeabilizers, such as cationic polypeptides, or of efflux system inhibitors, currently under development, would be one solution to the lack of activity of this antibiotic against *P. aeruginosa* [27].

Faropenem is not likely to select for efflux-mediated carbapenem resistance. Although faropenem is pumped out by the MexAB-OprM efflux system, it appears to have a distinct binding site since it does not interact with other MexAB-OprM substrates (i.e., β-lactams, β-lactamase inhibitors, quinolones, chloramphenicol, sulphamethoxazole, novobiocin) [4]. Thus, it may be said that the therapeutic use of faropenem has no reason to affect the susceptibility to imipenem and meropenem in the treatment of hospital-acquired infections caused by non-fermenting Gram-negative bacilli [4].

Lastly, in relation to cross-resistance between this penem and other β-lactam antibiotics, it has been observed that, in respiratory pathogens, such as *S. pneumoniae* and *H. influenzae*, the higher the resistance to penicillins, the lower the activity of faropenem [6, 9, 20, 23, 28]. In most cases, said cross-resistance is determined by PBPs alteration so that in *M. catarrhalis*, in which the predominant mechanism of resistance is the activity of β-lactamase, this phenomenon is less remarkable [6].

Pharmacology

Bioavailability of faropenem is approximately 70-80%. It binds to plasma proteins in about 90-95% and the theoretical volume of distribution is low. Its C_{max} and T_{max} are 13-14 mg/l and 1-2 hours, respectively, after a single dose of 300 mg and its administration with food does not alter its C_{max} or AUC. Faropenem medoxomil is hydrolized to faropenem after absorption and no evidence is available on the production of metabolites with antimicrobial activity. Faropenem elimination half-life is approximately 1 hour. Elimination is mainly by renal tubular secretion and 14-20% of the dosage administered may be recovered in urine. Age and sex do not affect faropenem half-life. In young adolescents (12-18 years) pharmacokinetic parameters are similar to those of young adults [17, 29-31].

Adverse Effects

The safety profile of faropenem, according to clinical trials carried out up to date, is excellent, with a minimum incidence of adverse effects, mainly gastrointestinal (although it is not associated to pseudomembranous colitis) which may be prevented by concomitant administration of faropenem with other antibiotics or the prior ingestion of probiotic agents that may maintain the balance of intestinal microbiota of the individual receiving the treatment [7, 12, 17, 23, 32]. Other slight effects, with an even lower incidence, were vaginal candidiasis and headaches [32].

Unlike what happens with carbapenems, faropenem does not have severe adverse effects such as cardiotoxicity or seizures [12, 23].

Clinical Indications

Faropenem has a wide spectrum of activity against both aerobic and anaerobic microorganisms and, unlike carbapenems and thanks to its good oral bioavailability, it is very useful in the treatment of community-acquired infections

Table 1.   *In Vitro* **Activity of Faropenem Against Various Human Pathogenic Bacteria [9,11,13,15,16,20-22,25,26,28]**

Microorganism	MIC$_{50}$ (in mg/L)	MIC$_{90}$ (in mg/L)
S. aureus		
MSSA	0.06-0.12	0.12
MRSA	2- >32	2- >32
Coagulase negative staphylococci	0.06-0.12	0.06-4
S. pneumoniae		
PSSP	≤0.004-0.016	0.008-0.03
PRSP	<0.12-1	0.5-2
Group A beta-haemolytic streptococci	0.015-0.03	0.015-0.03
Group B beta-haemolytic streptococci	0.03-0.06	0.03-0.06
Viridans **group streptococci**	0.12	1
E. faecalis	1	2-8
E. faecium	>32- 64	>32- >128
N. gonorrhoeae	0.03-0.06	0.06-0.25
N. meningitidis	0.008	0.008
Corynebacterium **spp.**	0.25	4
H. influenzae	0.25-0.5	0.5-1
Beta-lactamase-negative	0.25-0.5	0.5-1
Beta-lactamase-positive	0.25-0.5	0.5-1
Moraxella **spp.**	0.03-0.12	0.125-1
Enterobacteriaceae		
Citrobacter **spp.**	0.5	4
Enterobacter **spp.**	2	16
E. coli	0.5	1
Klebsiella **spp.**	0.5	2
M. morganii	1-4	2-8
Proteus **spp.**	1	4
Providencia **spp.**	2	8
Salmonella **spp.**	0.5	0.5
Serratia **spp.**	2	32
Shigella **spp.**	0.5	0.5
P. aeruginosa	32- >128	32- >128
Acinetobacter **spp.**	4-32	8- >32
B. cepacia	16	>32
S. maltophilia	32- >128	32- >128
Bacteroides **spp.**	0.25-2	0.25-4
Fusobacterium **spp.**	≤0.015-0.5	0.06-1
Prevotella **spp.**	0.06-0.25	0.5-1
Peptostreptococcus **spp.**	0.06-0.125	0.12-1

(Table 1. Contd….)

Microorganism	MIC$_{50}$ (in mg/L)	MIC$_{90}$ (in mg/L)
Porphyromonas **spp.**	≤0.015-0.12	0.06-1
C. difficile	4-8	8-16
C. perfrigens	0.5	0.5-1
P. acnes	0.06	1
Veillonella **spp.**	0.25	4
Actinomyces **spp.**	0.06	0.5

[22, 24, 26, 28, 33]. This is why, after its marketing, faropenem may be indicated in the treatment of community-acquired infections, especially acute bacterial sinusitis, acute exacerbations of chronic bronchitis, community-acquired pneumonia and slight skin and soft tissue infections (including those derived from bites) [17, 24, 26].

However, in October 2006 the FDA declared its dissatisfaction with the clinical trials carried out till then. According to the reported, clinical trials carried out in patients suffering from acute bacterial sinusitis and with exacerbations of chronic bronchitis should have been contrasted with placebo groups. In addition, samples from patients with community-acquired pneumonia were not considered valid and, lastly, there was not sufficient evidence on the effectiveness of faropenem in the treatment of skin and soft tissue infections [24].

DALBAVANCIN

Structure

Dalbavancin (BI-397) or 5,31-dichloro-38-demethoxycarbonyl-7-demethyl-19-deoxy-56-O-[2-deoxy-2-[(10-methyl-1-oxoundecanoyl)amino]-b-D-glucopyranosyl]-38-[[[3-dimethylamino)propyl]amino]carbonyl]-42-O-D-mannopyranosyl-N15-N-methyl-ristomycin-aglycon (Fig. **2**) is a semisynthetic glycopeptide for parenteral use derived from a natural molecule synthesized by *Nonomuria* spp. and structurally related with teicoplanin [34-37]. It is produced in three stages. First, the N-acylaminoglucuronic acid function was selectively esterified by incubation in methanol in the presence of sulphuric acid at 0-58C for 24 h. Second, the peptide-carboxy group was amidated with 3-dimethylamino-1-propylamine in dimethylsulphoxide in the presence of benzotriazolyloxy-tris-pyrrolidinophosphoniumhexafluoro-phosphate. Finally, the sugar methyl ester was saponified with 15% sodium hydroxide, with the resultant compound being dalbavancin [35, 36]. The differences with teicoplanin appear in apoliproteins 1 and 3, as well as in the number and position of sugar moieties, chlorine molecules and various methyl and hydroxyl groups. Thus, the molecule improves its activity without altering the underlying D-alanyl-D-alanine backbone, which is fundamental in the antimicrobial activity of this antibiotic [36].
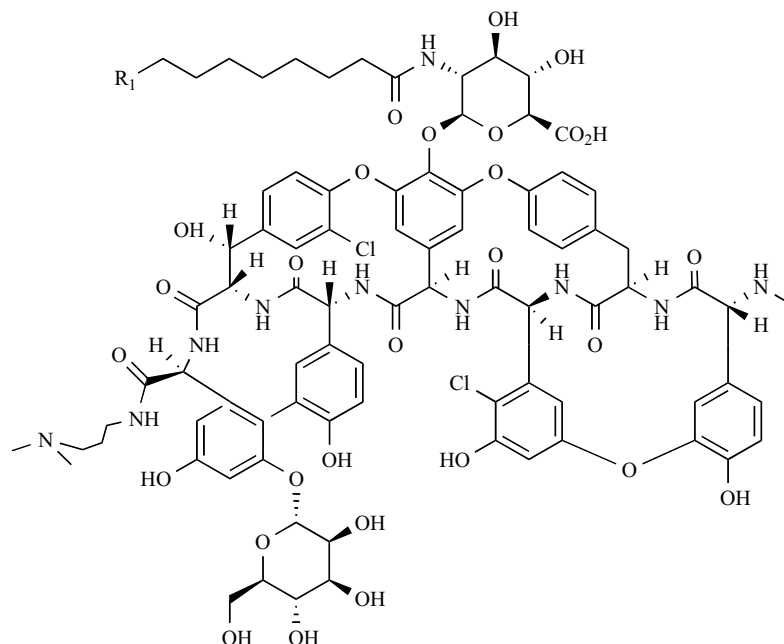

Fig. (2). Structure of dalbavancin.

Mechanism of Action

Glycopeptides inhibit bacterial wall synthesis by preventing the synthesis of peptidoglycan [38]. They present affinity for the D-alanine-D-alanine residue of the carboxy-terminal end of peptidoglycan precursors and thus prevent their binding. Consequently, there is an accumulation of precursors and the inhibition of reactions catalyzed by transpeptidases and carboxypeptidases, which do not recognize the substrates needed for synthesizing the peptidoglycan, takes place [34, 37].

The high affinity and antibiotic potential of dalbavancin are also based on a particular ability for dimerization and binding of the antibiotic to the lipophylic lateral chains that are in the bacterial membrane. Thus, this glycopeptide shows an *in vitro* bactericide activity against resistant Gram-positive bacteria that is stronger than that of vancomycin and teicoplanin [34, 35].

Spectrum of Activity

Its *in vitro* spectrum of activity is similar to that of other glycopeptides. However, dalbavancin has demonstrated favourable *in vitro* activity against MSSA, MRSA, VISA, VRSA, and linezolid-resistant *S. aureus*, as well as against methicillin-resistant coagulase-negative staphylococci and intermediate-resistant glycopeptides [36, 39]. Similarly, dalbavancin is more active than teicoplanin and vancomycin against streptococci, including multiresistant *S. pneumoniae* [34-46].

Regarding enterococci, and similarly to what happens with teicoplanin, dalbavancin is more active than vancomy-

Table 2.   *In Vitro* **Activity of Dalbavancin, Oritavancin and Telavancin Against Various Human Pathogenic Bacteria [40-46,68-73,97-101]**

Microorganism	Dalbavancin		Oritavancin		Telavancin	
	MIC$_{50}$ (in mg/L)	MIC$_{90}$ (in mg/L)	MIC$_{50}$ (in mg/L)	MIC$_{90}$ (in mg/L)	MIC$_{50}$ (in mg/L)	MIC$_{90}$ (in mg/L)
S. aureus						
Methicillin-susceptible	0.06-0.12	0.06-0.12	2	4	0.25-0.5	0.25-0.5
Methicillin-resistant	0.03-0.12	0.06-0.12	2	4	0.25	0.25-0.5
Coagulase-negative staphylococci						
Methicillin-susceptible	0.03	0.06	1	2	0.25	0.25-0.5
Methicillin-resistant	0.03	0.06	1	2	0.25-0.5	0.25-1
S. pneumoniae						
Penicillin-susceptible	≤0.016	0.016-0.03	0.004-0.03	0.008-0.125	0.016	0.016-0.03
Penicillin-resistant	≤0.016	≤0.016-0.03	0.004-0.03	0.015-0.125	0.015	0.03
MDRSP	≤0.016	0.016-0.03	-	-	0.015	0.03
S. pyogenes	≤0.03	≤0.03	0.12	0.25	0.03-0.125	0.03-0.125
S. agalactiae	≤0.03-0.06	≤0.03-0.125	-	-	0.06-0.125	0.06-0.125
***Viridans* group streptococci**	≤0.016-0.25	0.016-0.5	-	-	0.03-0.06	0.06-0.12
E. faecalis						
Vancomycin-susceptible	0.03	0.06	0.5	1	0.25-0.5	0.5-1
Vancomycin-resistant	4-32	32	-	-	2-4	4-8
E. faecium						16
Vancomycin-susceptible	0.06	0.12	0.06-0.12	0.25-0.5	0.12-0.25	0.25-0.5
Vancomycin-resistant	16	32	1	2	1-2	2-4
***Corynebacterium* spp.**	0.12-0.25	0.25-1	-	-	0.03	0.06
L. monocytogenes	-	-	-	-	0.125	0.125
***Actinomyces* spp.**	0.025	0.5	-	-	0.25	0.25
***Clostridium* spp.**	0.03-0.125	0.5-2	0.5	1	0.25	8
***Eubacterium* spp.**	0.25	1	-	-	0.125	0.25
***Propionibacterium* spp.**	0.25	0.5	0.125	0.25	0.06	0.125
***Peptostreptococcus* spp.**	0.125	0.25	0.125	0.5	0.06	0.25

cin against vancomycin-susceptible enterococci and against enterococci with VanB and VanC phenotypes; however, it is not active against VanA enterococci [34-39, 41, 45, 47-49]. Additionally, it was observed that activity against *E. faecium* is slightly lower than against *E. faecalis* and *E. hirae* [39, 41, 46, 49].

Other Gram-positive dalbavancin-susceptible bacteria are *Actinomyces* spp., *Bacillus* spp., *Corynebacterium* spp., *Clostridium* spp. (except for *C. clostridoforme*), *Eubacterium* spp., *Lactobacillus* spp. (except *L. acidophilus* and *L. casei*), *Listeria* spp., *Micrococcus* spp., *Peptostreptococcus* spp. and *Propionibacterium* spp. [34,36,39,41,44]. On the contrary, dalbavancin does not show any activity against Gram-negative bacteria, including anaerobic bacteria [34, 39].

Table **2** shows MIC_{50} and MIC_{90} values obtained *in vitro* against some human pathogenic bacteria.

Resistance

Enterococci were divided into several phenotypes based on their degree of resistance, induction and transference of resistance to vancomycin and teicoplanin. In all of them, resistance is owed to the synthesis of a precursor that is different from the D-alanine-D-alanine dipeptide, which may be D-alanine-D-lactate or D-alanine-D-serine [37].

Enterococci with VanA phenotype have a high degree of resistance to vancomycin (MIC ≥ 64 mg/l) and to teicoplanin (MIC ≥ 16 mg/l), a resistance which may be induced by both glycopeptides. Genes producing this phenotype are located within the Tn1546 transposon integrated in self-transferable plasmids. Transfer of these plasmids to other sensitive enterococci isolates or to other Gram-positive bacteria, such as *S. pyogenes* and *L. monocytogenes*, or even to *S. aureus,* has been proven [48].

Isolates with VanB phenotype show moderate resistance to vancomycin (MIC of 32-64 mg/l) and they remain sensitive to teicoplanin (MIC ≤ 1 mg/l). This resistance is not transferable and the gene involved is chromosomal. Resistance may only be induced by vancomycin but not by teicoplanin [48]. Isolates with VanC phenotype are moderately resistant to vancomycin (MIC of 8-32 mg/l) but sensitive to

teicoplanin (MIC ≤ 1 mg/l). It is a constituting, non-transferable resistance [48]. A VanD phenotype has also been described [48].

In staphylococci, on the other hand, resistance to glycopeptides is attributable to the abnormal structure of the cell wall, due to an increase in peptidoglycan production, which results in an abnormal thickening of the wall, thus limiting the binding of these antibiotics to their target [37, 48]. However, the existence of MRSA isolates with a high degree of resistance to glycopeptides that acquired the Tn1546 transposon have been proven [48].

Notwithstanding, no case of resistance to dalbavancin was observed [36]. In addition, *in vitro* resistance tests in staphylococci have not obtained mutants that are resistant to this antibiotic, a fact which proves the low power of selection of resistances, in comparison to teicoplanin and vancomycin [50, 51]. For Lefort *et al.*, this would be explained by the strong activity of dalbavancin against GISA isolates, the high serum drug concentration/MIC ratio and the persistent activity against the teicoplanin-resistant derivative [52]. However, as pointed out by Bennett *et al.*, available data are limited because they are not from isolates subjected to prolonged therapeutic levels of the antibiotic [39].

Pharmacology

The pharmacokynetics of dalbavancin is linear and proportional to the dosage, as may be derived from studies carried out in healthy volunteers and in a dosage range between 140 and 1120 mg. Table **3** shows the main pharmacokinetic parameters of this antibiotic after the administration of 1 gram on day 1 and 500 mg on day 8, due to a prolonged half life (6 to 10 days). C_{max} is achieved 30 minutes after administration and plasma concentration of dalbavancin is maintained over MIC_{90} of resistant isolates of staphylococci and streptococci for at least 12 days [53, 54]. Total distribution volume is 15.7 l at steady-state, with 4.5 l in the central compartment and 11.4 l in the peripheral compartment [55]. Binding to plasma proteins is 93%. Dalbavancin is excreted by renal and non-renal pathways; approximately 42% of the dosage administered is excreted unaltered in urine [54]. Estimated clearance is 0.06 l/h [55]. Faecal concentration of dalbavancin is 6.8-73.4 mg/kg (day 5) and 7.4-26.4 (day 14)

Table 3. Pharmacokinetics of Dalbavancin and Telavancin [54,74]

Parameter	Dalbavancin	Telavancin		
		5 mg/kg	10 mg/kg	12.5 mg/kg
C_{max} (mg/l)	278.3 (day 1) 166.3 (day 8)	44.9 ± 3.2	87.5 ± 6.0	112.0 ± 18.0
$AUC_{0-\infty}$ (mg*h/l)	33851	426 ± 49	859 ± 109	1143 ± 195
Vd_{ss} (l)	18.3 (day 8)	106 ± 5	115 ± 6	116 ± 13
Cl (l/min)	0.0466	11.9 ± 1.5	11.8 ± 1.4	11.3 ± 2.3
$T_{1/2}$ (h)	321	6.9 ± 0.6	7.5 ± 0.9	7.9 ± 0.9

C_{max}: maximum plasma concentration, AUC: area under the curve concentration-time, Vd_{ss}: apparent volume of distribution at steady state, Cl: total clearance, $T_{1/2}$: terminal plasma half-life.

after a 1 gram dose [56]. Pharmacokinetic parameters are similar in patients with slight kidney failure and in healthy volunteers, so no dose adjustment is required. Neither is dose adjustment required in patients with slight (class A Child-Pugh), moderate (class B Child-Pugh) or severe (class C Child-Pugh) liver failure [54].

Adverse Effects

Dalbavancin was generally well tolerated during the clinical trial phase [57]. The most common adverse effects were fever (18.2-50%), headaches (1.9-25%), diarrhoea (2.5-21.2%), low blood pressure (21.2%), anaemia (18.2%), dyspnoea (15.2%), oral and vaginal candidiasis (12.1%), insomnia (12.1%), nausea (3.2-9.1%) and skin reaction at the site of the injection (2.8%) [57-60]. Amongst the most severe, though less frequent, adverse effects were leucopaenia, moderate hyperglycaemia and severe pancytopaenia, which spontaneously cleared up. Similarly, alterations were not frequent in lab parameters: LDH elevation, ALT elevation and thrombopaenia. No case of red man syndrome was observed [57-59].

The neurotoxicity and ototoxicity observed with other glycopeptides were not observed during treatment with dalbavancin [59, 61]. According to Nord *et al.*, contrary to what happens with most antibiotics, the use of dalbavancin does not significantly affect human intestinal microbiota [56].

Clinical Indications

In vivo activity of dalbavancin against MSSA and MRSA in the rat granuloma pouch infection model, endocarditis caused by vancomycin-susceptible staphylococci and VISA, and pneumonia caused by penicillin resistant *S. pneumoniae* was proven in animal experiments [34, 36, 37, 39].

Its utility against skin and soft tissue infections caused by Gram-positive bacteria, as well as in sepsis related to colonization of catheters by coagulase-negative staphylococci,

MSSA or MRSA was confirmed in humans [34, 36, 39]. Other possible future applications of dalbavancin may be endocarditis, osteomyelitis, diabetic foot and respiratory infections [62].

TELAVANCIN

Structure

Telavancin (TD-6424) (Fig. **3**) is a bactericidal lipoglycopeptide with multiple mechanisms of action currently under clinical development (phase III studies). It is a vancomycin derivative obtained through the alkylation of the vancosamine substituent with a lateral hydrophobic chain (decyl-aminopropyl) and the presence of an aminomethyl substituent (phosphonomethyl) on the cyclic peptidic core at the resorcinol position [63-65]. These new incorporations to the molecule confer it improved activity against MRSA isolates and VanA phenotype enterococci, in addition to improving the pharmacokinetics of the antibiotic [63].

Mechanism of Action

Telavancin inhibits the cell wall synthesis with a potence that is 10 times higher than that of vancomycin. Telavancin inhibits bacterial cell wall synthesis through tight binding of the aglycone core structure to D-alanine-D-alanine-containing peptidoglycan precursor, lipid II, and nascent noncrosslinked peptidoglycan intermediates, thus inhibiting late stages of cell wall biosynthesis [64]. Notwithstanding, unlike vancomycin, telavancin does not only act at this level and its mechanism of action is more complex: telavancin interacts with the Gram-positive bacterial membrane to effect changes in membrane potential and permeability in a concentration-dependent manner, in a process mediated by the decylaminoethyl lateral chain [63-67]. This multimodal action mechanism, dependent on the antibiotic concentration, is responsible for the improvement of its activity against staphylococci (including MRSA, GISA, hGISA and VRSA isolates),
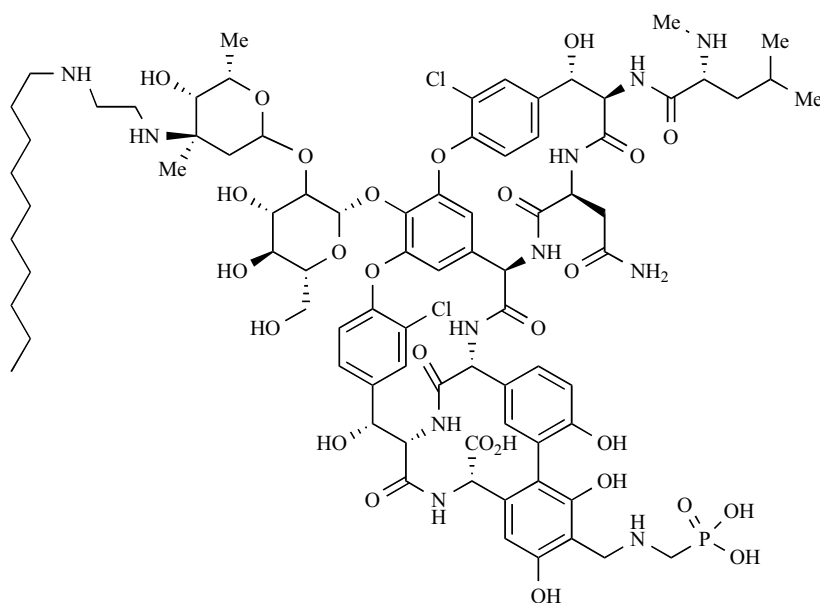

Fig. (3). Structure of telavancin.

S. pneumoniae (including MDRSP) and VanA enterococci, among others [63, 65].

Spectrum of Activity

Telavancin is active against an ample group of Gram-positive pathogens such as staphylococci (MSSA, MRSA, hVISA, VISA, VRSA isolates, those resistant to linezolid or daptomycin, MSCoNS, MRCoNS, vancomycin/teicoplanin-resistant *S. epidermidis* and biofilm-producing staphylococci); β and α haemolytic streptococci and, especially, against *S. pneumoniae* (including multiresistant isolates); enterococci (both susceptible and resistant to vancomycin); *L. monocytogenes* and some species of *Lactobacillus* spp., including vancomycin, linezolid or daptomycin resistant isolates (except for *L. casei*) [67-73]. It also shows activity against Gram-positive anaerobic bacteria, such as some species of the *Clostridium* spp. (mainly *C. difficile*, *C. perfrigens* and *C. ramosum*), *Eubacterium* spp., *Propionibacterium* spp. and *Peptostreptoccus* spp. [63]. However, like other glycopeptides, it is not active against Gram-negative bacteria [63, 65].

It has also been proven that co-administration of telavancin with cefepime, imipenem or piperacillin-tazobactam produces a synergic effect against VISA and VRSA isolates. The clinical use of these combinations is yet to be determined [65].

Table **2** reflects the *in vitro* activity of telavancin against some of the abovementioned microorganisms.

Resistance

Telavancin shows a low potential for the selection of resistant isolates among *S. aureus*, enterococci (including VRE) and multiresistant *S. pneumoniae*. The determinants of *van* resistance present in enterococci and staphylococci have relatively little effect on the activity of telavancin, mainly increasing MIC values in 2-4 times [65].

Pharmacology

The pharmacokinetics of telavancin is linear and dose-independent when administered once a day, for 7 days, in a range of 7.5 to 15 mg/kg of weight [74, 75]. The mean values of the pharmacokinetic parameters for telavancin are listed in Table **3**. It binds to plasma proteins in about 93% [74, 76]. Its penetration in skin blister fluids is approximately 40% of plasma levels [77]. A maximum concentration of 3.7 mg/l is obtained in pulmonary epithelial fluid and 45 mg/l in alveolar macrophages, while it lasts with concentrations of 42 mg/l up to 24 hours after start of administration. In addition, its activity is not affected by the pulmonary surfactant [78]. Its elimination is mainly renal and two thirds of the dosage administered are collected unaltered in urine in 48 hours [74, 75].

Clearance in healthy volunteers aged 65 and over was similar to that in young adults, although with a higher distribution volume and a longer half life [65]. Pharmacokinetic parameters are similar in men and women [75]. Creatinine clearance is related to telavancin clearance in patients with slight or moderate renal failure, and the AUC and $T_{1/2}$ increase such that adjustment of the dosage is advised in patients with moderate or severe renal failure [65]. In patients

with moderate liver failure (Child-Pugh class B) the pharmacokinetic parameters are equivalent to those of patients with normal liver function [65].

Adverse Effects

In general, treatment with telavancin seems to be well tolerated [63,67]. The most frequent adverse effects observed during clinical trials were slight to moderate in nature, and we may highlight the alteration of taste in 14-75% of individuals treated (reversible after 24-31 hours) and headaches (8-40%). Other effects were vertigo (35%), procedural site reaction (25%), nausea (13-20%), insomnia (13%), psychiatric disorders (10%), vomiting (8%), dyspnoea (7%), itching (6%), constipation (3-5%) and paresthesia (4%) [78-80].

High levels of serum creatinine were detected in some cases, as well as cases of slight and reversible hypopotasemia [78-80]. No cases of QTc interval lengthening were observed [79]. According to Barriere *et al.*, the use of telavancin entails minimal risk of adverse cardiac effects [81].

Telavancin is accumulated in lysosomes of eukaryote cells, and so it can be active against intracellular pathogens. However, and unlike oritavancin, it does not significantly affect cell levels of phospholipids and cholesterol, maybe due to a different accumulation rate or because of an intrinsic capacity to interfere with the lipidic metabolism of both molecules [82].

Clinical Indications

Up to the current moment, the use of telavancin has been proposed for the treatment of infections caused by staphylococci (including VRSA isolates): endocarditis, skin and soft tissue infections [83-85], peritoneal dialysis-associated peritonitis [86], pneumonias [87, 88], bacteraemias [89], osteomyelitis [90]; and, as monotherapy, in the treatment against meningitis caused by penicillin-resistant *S. pneumoniae* [91].

ORITAVANCIN

Structure

Oritavancin (LY333328) (Fig. **4**) is the N-substituted p-chlorophenylbenzyl derivative of chloroeremomycin, a natural glycopeptide product of *Amycolatopsis orientalis* fermentation [92, 93]. Oritavancin was obtained by reductive alkylation with 4'chloro-biphenylcarboxaldehyde of the natural glycopeptide chloroeremomycin, which differs from vancomycin by the addition of a 4-epi-vancosamine sugar and the replacement of the vancosamine by a 4-epi-vancosamine [94]. The addition of the lateral p-chlorophenylbenzyl chain to the structure of precursor chloroeremomycin confers an improved activity against enterococci, both VSE and VRE isolates, although it slightly reduces the activity against staphylococci [92].

Mechanism of Action

Like the rest of glycopeptides, oritavancin produces its effect through the inhibition of the cell wall synthesis, blocking peptidoglycane biosynthesis. The greater capacity for dymerization and the anchoring of the chlorobiphenyl side chain into the cytosolic membrane improve interaction and thus the activity of oritavancin with regards to vancomycin.
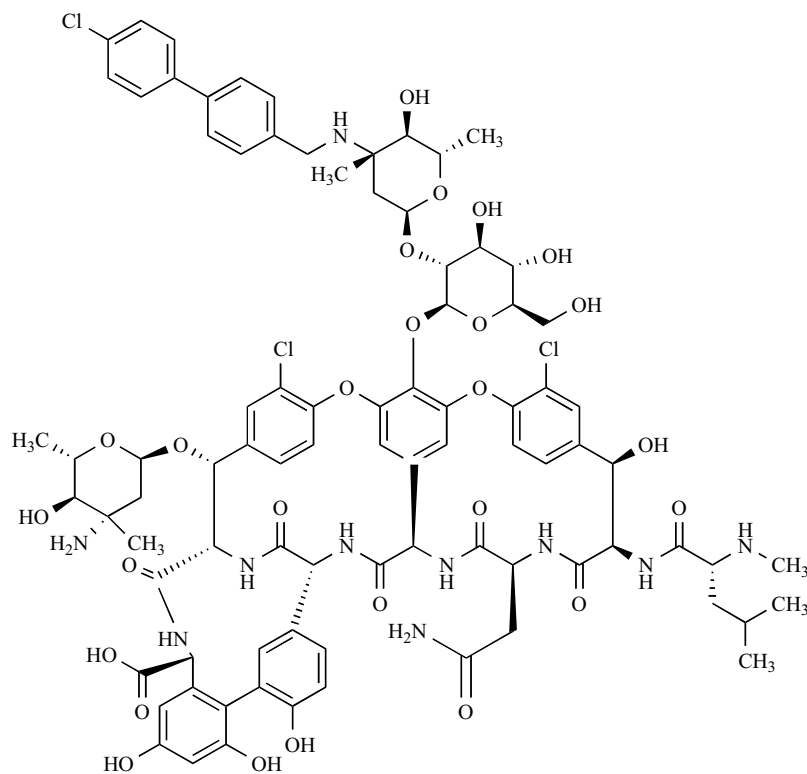
Fig. (4). Structure of oritavancin.

In fact, oritavancin also has the capacity to inhibit the synthesis of the cellular wall in vancomycin-resistant *Enterococcus* spp. isolates [92].

Although the bactericide activity of oritavancin against bacteria in the exponential phase is well established, Belley *et al.* explain that oritavancin induces depolarization of the membrane in MSSA isolates, thus increasing permeability and causing additional alterations in the stationary phase. This may explain the power of oritavancin against MSSA, MRSA and VRSA at minimal biofilm eradication concentrations (MBECs) between 0.5 and 8 mg/l [95].

Spectrum of Activity

Oritavancin shows a wide spectrum of activity, comparable to that of vancomycin, but with improved activity against certain microorganisms [3, 37]. It is active against Gram-positive bacteria, such as staphylococci (including MRSA and VRSA), streptococci (including MDRSP isolates) and enterococci (including VRE isolates or *E. gallinarum* and *E. casseliflavus* isolates with VanC phenotype) [96-101]. However, it may be noted that activity against VRE isolates may be slightly reduced in the stationary phase [93]. Other oritavancin-susceptible Gram-positive bacteria are *E. rhusiopathiae*, *L. monocytogenes* (including vancomycin-resistant isolates), *C. jeikeium*, *B. cereus* and *B. anthracis* [92, 102].

The administration of oritavancin in combination with gentamicin increases the bactericide activity against *E. faecalis*, in addition to preventing the appearance of resistance against both antibiotics [103]. The synergy between ori-

tavancin and other antibiotics such as linezolid, moxifloxacin and rifampicin against *S. aureus* isolates has also been recently proven [104].

Oritavancin is also active against anaerobic Gram-positive microorganisms, such as some species of the *Pediococcus* spp., *Peptostreptococcus* spp., *P. acnes* and *C. perfringens* types [92, 97], and its effectiveness in the treatment of infections caused by *C. difficile* was recently demonstrated [105].

On the other hand, oritavancin, like other glycopeptides, has no activity against Gram-negative pathogens [3] or against mycobacteria [92].

Table **2** shows MIC_{50} and MIC_{90} values obtained *in vitro* for oritavancin against some of the abovementioned microorganisms.

Resistance

Up to date, no specific *in vivo* resistance or high degrees of *in vitro* resistance to oritavancin have been detected [92, 99]. In addition, this antibiotic may be able to evade the mechanisms of resistance to glycopeptides from staphylococci and enterococci [37]. In fact, its acceptable activity against VRE isolates is due to the close binding between the antibiotic and the D-Ala-D-Lac residues [92]. Notwithstanding, enterococci with VanA and VanB phenotypes show reduced susceptibility to the glycopeptide, either due to the overexpression of resistance determinants or to the reduction in the levels of D-Ala-D-Ala precursors [92, 93]. Studies carried out on oritavancin show that the poor capacity to induce resistance exercised by the glycopeptide on these

phenotypes would be enough to influence the susceptibility of the isolates against this antibiotic [92].

Pharmacology

Following a short, constant-rate infusion, the pharmacokinetics of oritavancin were linear across a total dose range from 3.66 to 44.6 mg. The mean plasma terminal half-life of oritavancin was 195.4 hours across all dose levels from 0.05 to 0.5 mg/kg. Median C_{max} for the 0.5 mg/kg dose group was 6.5 mg/l. AUC also increased in proportion to dose and the median $AUC_{0-\infty}$ for the 0.5 mg/kg dose group was 68.3 mg*h/l. Renal clearance was approximately 0.46 ml/min. Less than 5% and 1% of administered drug were recovered in the urine and faeces, respectively, 7 days after a single dose [106]. Mean drug concentrations in blister fluid exceed the oritavancin MIC at which 90% of *S. aureus* strains are inhibited by approximately 2 to 5.5-fold at 12 h and 1.5 to 3-fold at 24 h following administration of both 200 mg once a day for 3 days and 800 mg as one single dose regimens [107].

Adverse Effects

According to the different clinical trials carried out to date, oritavancin is a well tolerated antibiotic. The adverse effects that appear are slight to moderate in nature, and the most common ones are headaches, rhinitis or dry skin. Other effects, such as abnormal dreams, insomnia, pharyngitis, itching, anxiety, conjunctivitis, diarrhoea, dyspnoea, ear disorder, ear pain, eczema, epistaxis, eye disorder, flatulence, malaise, nail disorder, paranoia, rash, rectal disorder, skin disorder, ulcerative stomatitis by herpes simplex, urinary retention and vertigo were much less frequent. Asymptomatic increase of transaminases was only observed in some cases, and with no significant variation in the levels of bilirubin. No abnormal values have been detected in activated partial thromboplastin time, anaphylactic reactions or loss of hearing [106].

Van Bambeke *et al*. noted the possibility that oritavancin has a negative effect on eukaryote cells due to the capacity of its intralisosomal accumulation. The accumulation of phospholipids and lisosomal alterations are known to be associated to kidney and hepatic failure in aminoglycosides, amiodarone and diethylaminoethoxyhexestrol [108].

Clinical Indications

Currently, oritavancin has positively gone through several clinical trials for the treatment of skin and soft tissue infections, as well as for the treatment of bacteraemia caused by Gram-positive bacteria [98]. Equally so, its effectiveness has been proven in the treatment of meningitis caused by *S. pneumoniae*, central venous catheter-associated infection by vancomycin-resistant *E. faecium* and endocarditis caused by MRSA and vancomycin-susceptible or resistant *E. faecalis* [93, 96].

Other possible applications are the use as adjunct to surgical management of lower extremity ulcerations [109] and as prophylaxis for first responders to anthrax threats, for postexposure prophylaxis and treatment in cases of known or suspected anthrax exposure, given the good activity of this glycopeptide against *B. anthracis* [102].

CEFTOBIPROLE

Structure

Ceftobiprole (BAL9141) (Fig. **5**) is a pyrrolidinone-3-ylidene-methyl cephalosporin of parenteral administration [110-112]. It is considered a fifth generation cephalosporin given its wide spectrum of action and especially due to its activity against MRSA isolates [113].
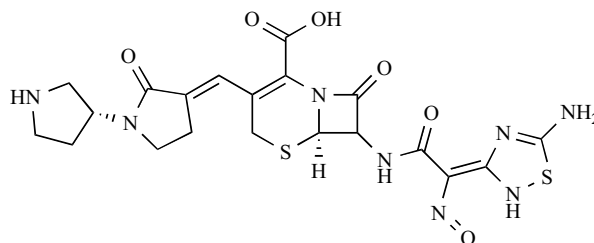

Fig. (5). Structure of ceftobiprole.

Mechanism of Action

Ceftobiprole, like the other β-lactam antibiotics, acts by inhibiting the cell wall synthesis through binding to PBPs [114]. However, what differentiates the capacity of this molecule from all the other antibiotics of its group is that it was designed with the capacity of binding with high affinity to altered PBPs responsible for the resistance against β-lactams in some species, such as PBP2a, responsible for resistance against methicillin in *Staphylococcus* spp., PBP2x responsible for resistance against penicillin in *S. pneumoniae*, as well as other PBPs in *E. coli* or *P. aeruginosa*, amongst other bacteria [113-116]. Specifically, the capacity of binding to PBP2a is related to the presence of a long hydrophobic lateral chain in position 3 in the molecule of ceftobiprole, which would facilitate a conformational change in PBP and the formation of a stable binding complex [113]. This high affinity would explain the wide antibacterial spectrum of ceftobiprole against Gram-positive and Gram-negative microorganisms [116].

Its inability to bind to *E. faecium* PBP5 is responsible for the high MIC values against this pathogen [114].

Spectrum of Activity

Ceftobiprole has a wide spectrum of activity which includes Gram-positive, Gram-negative and anaerobic pathogens [117-119]. This fact allows its application as monotherapy in the treatment of severe hospital and community acquired infections [120, 121].

It is active against staphylococci (MSSA, MRSA, VISA, VRSA, methicillin-susceptible and methicillin-resistant CoNS and vancomycin-intermediate CoNS), streptococci (MDRSP included, although its activity reduces as MIC values for β-lactam antibiotics increase), enterococci (ampicillin/vancomycin-resistant and β-lactamase producing *E. faecalis*, but not against *E. faecium*) and *Listeria* spp. [119-135].

Ceftobiprole is equally active against the *Enterobacteriaceae* family (except for ESBLs or carbapenemase-producing isolates), *H. influenzae* and *M. catarrhalis* (including β-lactamase-producing isolates), *Neisseria* spp. and *P. aeruginosa* (depending on the degree of β-lactam resistance)

[128-137]. On the other hand, its activity is scarce against other non-fermenting bacilli such as *Acinetobacter* spp., *S. maltophilia* and *B. cepacia* [113, 128, 132].

Ceftobiprole is also active against *Corynebacterium* spp., *Lactobacillus* spp., *Bacillus* spp., *Actinomyces* spp., *Clostridium* spp., *Fusobacterium* spp., *Peptostreptococcus* spp. (except *P. anaerobius*), *Porphyromonas* spp. or *Propionibacterium* spp. [113, 129, 131, 138, 139]. However, its activity against *Bacteroides* spp. and *Prevotella* spp. is far more limited [128, 129, 131, 135].

Table **4** shows *in vitro* MIC values for ceftobiprole against some of the above-mentioned microorganisms.

Resistance

Ceftobiprole is capable of evading the usual resistance mechanisms against β-lactam agents due to its high binding affinity to abnormal PBPs [110, 112, 126, 135]. Notwithstanding, recently Banerjee *et al*. described the existence of several mutations in the *mecA* gene, PBP2a codifier, which would confer resistance against ceftobiprole in specific MRSA isolates [140].

On the other hand, this antibiotic is relatively stable against type C β-lactamases and it is a low inductor of their expression or unrepression [117, 135]. However, like with other cephalosporins, ceftobiprole may become inactive through the action of derepressed AmpC, class A cephalosporinases, ESBLs and metallo-β-lactamases [114, 119].

Pharmacology

The pharmacokinetics of ceftobiprole are linear following single and multiple infusions of 125-1000 mg. After its intravenous administration, it transforms into a diacetyl compound, the active form of the antibiotic, through the action of plasma sterases. Binding to plasma proteins, mainly to albumin and to α_1-acid glycoprotein, is approximately 16% and independent of the drug and protein concentrations. Its apparent distribution volume at steady-state approximately corresponds with the volume of the extracellular fluid compartment in the adult individual (18.2 l). Ceftobiprole undergoes minimal hepatic metabolism, and the primary metabolite is the beta-lactam ring-opened hydrolysis product (open-ring metabolite). Ceftobiprole does not significantly induce or inhibit relevant cytochrome P450 enzymes and is neither a substrate nor an inhibitor of P-glycoprotein. The predominant mechanism responsible for elimination is glomerular filtration, with approximately 89% of the dose being excreted as the prodrug, active drug (ceftobiprole) and open-ring metabolite. Renal clearance of the free fraction is approximately equal to the normal glomerular filtration rate in adults (125 ml/min). Studies with multiple doses have not shown drug accumulation. The pharmacodynamics of ceftobiprole are similar in males and females, and dosing adjustments are not required based on gender. In patients with moderate to severe renal impairment, systemic clearance of ceftobiprole correlated well with creatinine clearance [141-143].

Adverse Effects

Treatment with ceftobiprole has shown to be safe and well tolerated in clinical trials [127, 135]. The incidence of adverse effects was comparable to that of other antibiotic groups [135, 144]. The most common ones observed were slight alterations in taste, nausea and vomiting. No ECG or relevant lab parameters were observed [142]. Ednie *et al*. have stated that, due to the fact that ceftobiprole activity against *C. difficile* is not optimum, cases of pseudomembranous cholitis may appear in the patients treated [138].

Clinical Indications

Up to date, and based on animal models, the use of ceftobiprole has been proposed for treatment of endocarditis caused by MRSA isolates [145], pneumonia caused by *H. influenzae*, *E. cloacae* and *K. pneumoniae* [146] and infections caused by multiresistant *E. faecalis* isolates [147].

This antibiotic has already successfully passed phase III for the treatment of skin and soft tissue infections and hospital-acquired pneumonia caused by MRSA [144] and is currently in phase III for its application for community-acquired pneumonia [123, 135].

ICLAPRIM

Structure and Mechanism of Action

Iclaprim (AR-100) (Fig. **6**) is an investigational racemate of 2,4-diaminopyrimidine composed by two enantiomers with similar antibiotic activities and which, like the rest of the diaminopyrimidines, acts on bacteria by selectively inhibiting the dihydrofolate reductase enzyme (DHFR) [148-150]. It has been observed that both iclaprim and trimetoprim preferably inhibit DNA and RNA synthesis, with scarce effect on the cell wall or protein synthesis [149].

Spectrum of Activity

Iclaprim is active against both Gram-positive and Gram-negative bacteria, including isolates resistant to other antibiotics [149, 151]. In addition, the administration together with sulfonamides shows synergic activity against both groups of bacteria, since they inhibit dihydropteroate synthetase (DHPS), the other enzyme involved in the folic acid pathway [150, 151].

Thus, this antibiotic is active against staphylococci (MSSA, MRSA, VISA, VRSA and macrolide, quinolone and trimethoprim-resistant isolates of *S. aureus*), streptococci (including penicillin-susceptible or resistant isolates, sulfamethoxazole-susceptible or resistant isolates, clarithromycin-susceptible and levofloxacin-resistant isolates of *S. pneumoniae*, as well as macrolide and clindamycin resistant isolates of *S. pyogenes* and *S. agalactiae*) and enterococci [148-154]. The presence of both enantiomers of the molecule is responsible for its high activity against sulfamethoxazole-susceptible and resistant isolates of *S. pneumoniae*, but its mechanism of action is unknown [150]. It is also active against Gram-negative bacteria, such as *E. coli*, *K. pneumoniae*, *P. vulgaris*, *Enterobacter* spp., *Neisseria* spp., *H. influenzae*, *M. catarrhalis*, *L. pneumophila*, *C. trachomatis* and *C. pneumoniae* [148, 149, 151, 155]. However, it is not active against *P. aeruginosa* [148]. Table **5** reflects the *in vitro* activity of iclaprim against some of the abovementioned microorganisms.

Table 4. *In Vitro* **Activity of Ceftobiprole Against Various Human Pathogenic Bacteria [110,112,122,124,128-132,137-139]**

Microorganism	MIC$_{50}$ (in mg/L)	MIC$_{90}$ (in mg/L)
S. aureus		
Methicillin-susceptible	0.25-0.5	0.5
Methicillin-resistant	0.5-2	1-2
Coagulase-negative staphylococci		
Methicillin-susceptible	0.125-0.25	0.25-1
Methicillin-resistant	0.5-1	2
S. pneumoniae		
Penicillin-susceptible	≤0.015-0.06	≤0.015-0.06
Penicillin-resistant	0.25-0.5	0.25-1
Macrolide-susceptible	0.25	0.5
Macrolide-resistant	0.5	1
Quinolone-susceptible	0.5	0.5
Quinolone-resistant	0.5	1
S. pyogenes	0.008	0.015
S. agalactiae	0.015-0.06	0.015-0.12
Viridans group streptococci	≤0.06	0.12-0.25
E. faecalis	0.5	0.5-4
E. faecium	32- >64	>32
Lactobacillus spp.	1	>128
Neisseria spp.	≤0.002	0.06
Enterobacteriaceae		
Citrobacter spp.		
AmpC (non-derep)	≤0.06	1
AmpC (derep)	2	>32
Enterobacter spp.		
AmpC (non-derep)	0.06	4
AmpC (derep)	8	>32
E. coli		
ESBLs⁻	0.03	0.06
ESBLs⁺	8- 32	8- >32
Klebsiella spp.		
ESBLs⁻	≤0.06-0.125	0.5- >8
ESBLs⁺	>8	>8
M. morganii	0.12	64
Proteus spp.		
ESBLs⁻	0.03	0.06
ESBLs⁺	>32	>32
Salmonella spp.	≤0.06-0.03	≤0.06-0.03
Serratia spp.	≤0.06	1-8
Shigella spp.	0.03	0.03
H. influenzae		
Beta-lactamase-negative	0.06	0.25
Beta-lactamase-positive	0.03	0.25

(Table 4. Contd….)

Microorganism	MIC$_{50}$ (in mg/L)	MIC$_{90}$ (in mg/L)
Moraxella **spp.**	≤0.06	0.12-0.5
Pseudomonas **spp.**	1-8	8- >64
Acinetobacter **spp.**		
A. baumannii	2	16
A. lwoffii	≤0.06	≤0.06
B. cepacia	8-32	64
S. maltophilia	32- >64	32- >64
Actinomyces **spp.**	0.06	8
Bacteroides **spp.**	8-16	32- >128
C. difficile	4	8
C. perfringens	≤0.016	≤0.016
Corynebacterium **spp.**	0.06	>32
Fusobacterium **spp.**	0.12	8
Peptostreptococcus **spp.**	0.25	32
Porphyromonas **spp.**	≤0.03-0.12	16
Propionibacterium **spp.**	0.06	0.125
Prevotella **spp.**	0.12-4	16- >128
Veillonella **spp.**	0.5	>128

Resistance

The resistance to trimethoprim in pathogens such as *S. aureus* and *S. pneumoniae* is due to a single mutation in DHFR active site, such that it loses the hydrogen bond essential for the interaction and binding to the antibiotic. However, iclaprim is able to continue binding to the mutated enzyme through an as yet unknown mechanism, which would explain its improved activity in comparison with trimethoprim [149, 150].
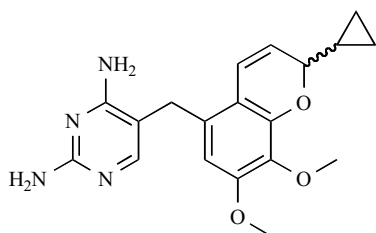

Fig. (6). Structure of iclaprim.

It may be noted that, in comparison to other antibiotic groups, the use of diaminopyrimidines for three decades has resulted in low bacterial resistance rates [149]. In addition, it has been proven that iclaprim has a lower capacity of selection of resistant isolates than trimethoprim [149, 150].

Pharmacology

Data on iclaprim are limited. Following single intravenous administration, the C_{max} and AUC of iclaprim increased proportionally to the dose, $T_{1/2}$ and clearance (2–4 h) were independent of dose. *In vitro* plasma protein binding of iclaprim was 92% to 94% over a wide range of concentrations. After a single dose of 1.6 mg/kg 60 min intravenous infusion, iclaprim concentrations in epithelial lining fluid and alveolar macrophages exceeded the MIC$_{90}$ for penicillin-susceptible, -intermediate and -resistant *S. pneumoniae* for 7, 7 and 4 h, respectively, and *C. pneumoniae* for 7 h. Mean

Table 5.   *In Vitro* **Activity of Iclaprim Against Gram-Positive and Gram-Negative Bacteria [151,154,155]**

Microorganism	MIC$_{50}$ (in mg/L)	MIC$_{90}$ (in mg/L)
S. agalactiae	-	0.25
S. pyogenes	-	0.06
C. pneumoniae	0.5	0.5
C. trachomatis	0.5	0.5
L. pneumophila	0.03	0.06

iclaprim concentrations in epithelial lining fluid exceeded the MIC$_{90}$ for *H. influenzae* and *M. catarrhalis* for up to 4 and 2 h, respectively. In alveolar macrophages, the MIC$_{90}$ was exceeded for up to 7 h. Furthermore, the MIC$_{90}$ for methicillin-resistant *S. aureus* of 0.12 µg/ml was exceeded at all sites for up to 7 h. The pharmacokinetic profile of this agent reveals that iclaprim is available for intravenous and oral use, with good oral bioavailability [153, 156].

Clinical Indications

Current phase III clinical trials for the therapeutic application of iclaprim in complicated skin and soft tissue infections have already finished. On the other hand, phase II clinical trials for the treatment of hospital-acquired pneumonia are currently under way. Both infectious process include MRSA isolates as aetiology agents [148, 153, 154, 157, 158]. Authors such as Kohlhoff *et al.* also point out the role that iclaprim may play against respiratory infections caused by *C. pneumoniae* and genital infections caused by *C. trachomatis* [151].

CONCLUSIONS

Bacterial resistance to antibiotics is consequence of the presence of genetic determinants capable, in some cases, of transferral between bacterias of the same or different species. An excessive and, in many cases, inappropriate, use of antibiotics in medical or veterinary sciences has resulted in a fast increase of the presence of multi-resistant microorganisms. From an assistential point of view, infections caused by them result, amongst others, in an increase in clinical complications which include the risk of suffering from a severe disease which, up to this date, may have been successfully treated, and longer periods of hospital stays. The situation is currently worrisome given that a point may be reached at which effective antibiotics may not be available to treat seriously sick patients suffering from infectious processes caused by these pathogens.

Thus, it is absolutely necessary that the pharmaceutical industry develops new antibiotics that may guarantee the availability of treatments effective against multi-resistant bacteria. In addition, it is also essential that these new drugs, like the ones preceding, be used in a more restricted manner and be always backed by solid medical knowledge.

REFERENCES

[1]   Bosso, J.A. The antimicrobial armamentarium: evaluating current and future treatment options. *Pharmacotherapy*, **2005**, *25*(10 Pt 2), 55S-62S.

[2]   Slama, T.G. Gram-negative antibiotic resistance: There is a price to pay. *Crit. Care*, **2008**, *12*(Suppl 4), S4.

[3]   Aksoy, D.Y.; Unal, S. New antimicrobial agents for the treatment of Gram-positive bacterial infections. *Clin. Microbiol. Infect.*, **2008**, *14*, 411-20.

[4]   Dalhoff, A.; Janjic, N.; Echols, R. Redefining penems. *Biochem. Pharmacol.*, **2006**, *71*, 1085-95.

[5]   Gao, S.; Chen, W.; Tao, X.; Miao, H.; Yang, S., Wu, R. Determination of faropenem in human plasma and urine by liquid chromatography-tandem mass spectrometry. *Biomed. Chromatogr.*, **2008**, *22*, 5-12.

[6]   Walsh, F.; Amyes, A.K.; Amyes, S.G. The *in vitro* effects of faropenem on lower respiratory tract pathogens isolated in the United Kingdom. *Int. J. Antimicrob. Agents*, **2003**, *21*, 581-4.

[7]   Ogura, K.; Mitsuno, Y.; Maeda, S.; Hirata, Y.; Yanai, A.; Shibata, W.; Ohmae, T.; Yoshida, H.; Kawabe, T.; Omata, M. Efficacy and safety of faropenem in eradication therapy of *Helicobacter pylori*. *Helicobacter*, **2007**, *12*, 618-22.

[8]   Saitoh, H.; Sawazaki, R.; Oda, M; Kobayashi, M. Region-dependent absorption of faropenem shared with foscarnet, a phosphate transporter substrate, in the rat small intestine. *Int. J. Antimicrob. Agents*, **2008**, *32*, 267-71.

[9]   Jones, R.N.; Critchley, I.A.; Whittington, W.L.; Janjic, N.; Pottumarthy, S. Activity of faropenem tested against *Neisseria gonorrhoeae* isolates including fluoroquinolone-resistant strains. *Diagn. Microbiol. Infect. Dis.*, **2005**, *53*, 311-7.

[10]   Dalhoff, A; Nasu, T; Okamoto, K. Target affinities of faropenem to and its impact on the morphology of Gram-positive and Gram-negative bacteria. *Chemotherapy*, **2003**, *49*, 172-83.

[11]   Critchley, I.A.; Brown, S.D.; Traczewski, M.M.; Tillotson, G.S.; Janjic, N. National and regional assessment of antimicrobial resistance among community-acquired respiratory tract pathogens identified in a 2005-2006 U.S. Faropenem surveillance study. *Antimicrob. Agents Chemother.*, **2007**, *51*, 4382-9.

[12]   Critchley, I.A.; Jacobs, M.R.; Brown, S.D.; Traczewski, M.M.; Tillotson, G.S.; Janjic, N. Prevalence of serotype 19A *Streptococcus pneumoniae* among isolates from U.S. children in 2005-2006 and activity of faropenem. *Antimicrob. Agents Chemother.*, **2008**, *52*, 2639-43.

[13]   Milatovic, D.; Schmitz, F.J.; Verhoef, J.; Fluit, A.C. *In vitro* activity of faropenem against 5460 clinical bacterial isolates from Europe. *J. Antimicrob. Chemother.*, **2002**, *50*, 293-9.

[14]   von Eiff, C.; Schepers, S.; Peters, G. Comparative *in vitro* activity of faropenem against staphylococci. *J. Antimicrob. Chemother.*, **2002**, *50*, 277-80.

[15]   Woodcock, J.M.; Andrews, J.M.; Brenwald, N.P.; Ashby, J.P.; Wise, R. The in-vitro activity of faropenem, a novel oral penem. *J. Antimicrob. Chemother.*, **1997**, *39*, 35-43.

[16]   Wexler, H.M.; Molitoris, D.; St Joh, S.; Vu, A.; Read, E.K.; Finegold, S.M. *In vitro* activities of faropenem against 579 strains of anaerobic bacteria. *Antimicrob. Agents Chemother.*, **2002**, *46*, 3669-75.

[17]   Gettig, J.P.; Crank, C.W.; Philbrick, A.H. Faropenem medoxomil. *Ann. Pharmacother.*, **2008**, *42*, 80-90.

[18]   Rodel, R.; Freyer, A.; Bittner, T.; Schafer, V.; Hunfeld, K.P. *In vitro* activities of faropenem, ertapenem, imipenem and meropenem against *Borrelia burgdorferi s.l. Int. J. Antimicrob. Agents*, **2007**, *30*, 83-6.

[19]   Mushtaq, S.; Hope, R.; Warner, M., Livermore, D.M. Activity of faropenem against cephalosporin-resistant *Enterobacteriaceae*. *J. Antimicrob. Chemother.*, **2007**, *59*, 1025-30.

[20]   Critchley, I.A.; Karlowsky, J.A.; Draghi, D.C.; Jones, M.E.; Thornsberry, C.; Murfitt, K.; Sahm, D.F. Activities of faropenem, an oral beta-lactam, against recent U.S. isolates of *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*. *Antimicrob. Agents Chemother.*, **2002**, *46*, 550-5.

[21]   du Plessis, M.; Capper, T.P.; Klugman, K.P. *In vitro* activity of faropenem against respiratory pathogens. *J. Antimicrob. Chemother.*, **2002**, *49*, 575-7.

[22]   Schmitz, F.J.; Boos, M.; Mayer, S.; Verhoef, J.; Milatovic, D.; Fluit, A.C. *In vitro* activity of faropenem and 20 other compounds against beta-lactamase-positive and -negative *Moraxella catarrhalis* and *Haemophilus influenzae* isolates and the effect of serum on faropenem MICs. *J. Antimicrob. Chemother.*, **2002**, *49*, 220-3.

[23]   Stone, K.C.; Dagan, R.; Arguedas, A.; Leibovitz, E.; Wang, E.; Echols, R.M.; Janjic, N.; Critchley, I.A. Activity of faropenem against middle ear fluid pathogens from children with acute otitis media in Costa Rica and Israel. *Antimicrob. Agents Chemother.*, **2007**, *51*, 2230-5.

[24]   Schurek, K.N.; Wiebe, R.; Karlowsky, J.A.; Rubinstein, E.; Hoban, D.J.; Zhanel, G.G. Faropenem: review of a new oral penem. *Expert Rev. Anti Infect. Ther.*, **2007**, *5*, 185-98.

[25]   Milazzo, I.; Blandino, G.; Caccamo, F.; Musumeci, R.; Nicoletti, G.; Speciale, A. Faropenem, a new oral penem: antibacterial activity against selected anaerobic and fastidious periodontal isolates. *J. Antimicrob. Chemother.*, **2003**, *51*, 721-5.

[26]   Goldstein, E.J.C.; Citron, D.M.; Merriam, C.V.; Warren, Y.A.; Tyrrell, K.L.; Fernandez, H.T. Comparative *in vitro* activity of faropenem and 11 other antimicrobial agents against 405 aerobic and anaerobic pathogens isolated from skin and soft tissue infec-

tions from animal and human bites. *J. Antimicrob. Chemother.*, **2002**, *50*, 411-20.

[27]   Okamoto, K.; Gotoh, N.; Nishino, T. *Pseudomonas aeruginosa* reveals high intrinsic resistance to penem antibiotics: penem resistance mechanisms and their interplay. *Antimicrob. Agents Chemother.*, **2001**, *45*, 1964-71.

[28]   Decousser, J.W.; Pina, P.; Picot, F.; Allouch, P.Y. Comparative *in vitro* activity of faropenem and 11 other antimicrobial agents against 250 invasive *Streptococcus pneumoniae* isolates from France. *Eur. J. Clin. Microbiol. Infect. Dis.*, **2003**, *22*, 561-5.

[29]   Gustafsson, I.; Cars, O. The influence of protein binding on the antibacterial activity of faropenem against *Haemophilus influenzae*. *Clin. Microbiol. Infect.*, **2004**, *10*, 934-7.

[30]   Boswell, F.J.; Ashby, J.; Andrew, J.M.; Wise, R. Effect of protein binding on the *in vitro* activity and pharmacodynamics of faropenem. *J. Antimicrob. Chemother.*, **2002**, *50*, 525-32.

[31]   Uchino, H.; Tamai, I.; Yabuuchi, H.; China, K.; Miyamoto, K.; Takeda, E.; Tsuji, A. Faropenem transport across the renal epithelial luminal membrane *via* inorganic phosphate transporter NPT1. *Antimicrob. Agents Chemother.*, **2000**, *44*, 574-7.

[32]   Upchurch, J.; Rosemore, M.; Tosiello, R.; Kowalsky, S.; Echols, R. Randomized double-blind study comparing 7- and 10-day regimens of faropenem medoxomil with a 10-day cefuroxime axetil regimen for treatment of acute bacterial sinusitis. *Otolaryngol. Head. Neck. Surg.*, **2006**, *135*, 511-7.

[33]   Dalhoff, A.; Thomson, C.J. The art of fusion: from penams and cephems to penems. *Chemotherapy*, **2003**, *49*, 105-20.

[34]   Chen, A.Y.; Zervos, M.J.; Vazquez, J.A. Dalbavancin: a novel antimicrobial. *Int. J. Clin. Pract.*, **2007**, *61*, 853-63.

[35]   Malabarba, A.; Goldstein, B.P. Origin, structure, and activity *in vitro* and *in vivo* of dalbavancin. *J. Antimicrob. Chemother.*, **2005**, *55*(Suppl. S2), ii15-ii20.

[36]   Pope, S.D.; Roecker, A.M. Dalbavancin: a novel lipoglycopeptide antibacterial. *Pharmacotherapy*, **2006**, *26*, 908-18.

[37]   Van Bambeke, F. Glycopeptides in clinical development: pharmacological profile and clinical perspectivas. *Curr. Opin. Pharmacol.*, **2004**, *4*, 471-8.

[38]   Gandolfi, R.; Jovetic, S.; Marinelli, F.; Molinari, F. Biotransformations of lipoglycopeptides to obtain novel antibiotics. *J. Antibiot.*, **2007**, *60*, 265-71.

[39]   Bennett, J.W.; Lewis, J.S.; Ellis, M.W. Dalbavancin in the treatment of complicated skin and soft-tissue infections: a review. *Ther. Clin. Risk Manag.*, **2008**, *4*, 31-40.

[40]   Biedenbach, D.J.; Ross, J.E.; Fritsche, T.R.; Sader, H.S.; Jones, R.N. Activity of dalbavancin tested against *Staphylococcus* spp. and β-hemolytic *Streptococcus* spp. isolated from 52 geographically diverse medical centers in the United States. *J. Clin. Microbiol.*, **2007**, *45*, 998-1004.

[41]   Gales, A.C.; Sader, H.S.; Jones, R.N. Antimicrobial activity of dalbavancin tested against Gram-positive clinical isolates from Latin American medical centres. *Clin. Microbiol. Infect.*, **2005**, *11*, 95-100.

[42]   Goldstein, E.J.C.; Citron, D.M.; Warren, Y.A.; Tyrrell, K.L.; Merriam, C.V.; Fernandez, H.T. *In vitro* activities of dalbavancin and 12 other agents against 329 aerobic and anaerobic Gram-positive isolates recovered from diabetic foot infections. *Antimicrob. Agents Chemother.*, **2006**, *50*, 2875-9.

[43]   Lin, G.; Credito, K.; Ednie, L.M.; Appelbaum, P.C. Antistaphylococcal activity of dalbavancin, an experimental glycopeptide. *Antimicrob. Agents Chemother.*, **2005**, *49*, 770-2.

[44]   Streit, J.M.; Fritsche, T.R.; Sader, H.S.; Jones, R.N. Worldwide assessment of dalbavancin activity and spectrum against over 6,000 clinical isolates. *Diagn. Microbiol. Infect. Dis.*, **2004**, *48*, 137-43.

[45]   Streit, J.M.; Sader, H.S.; Fritsche, T.R.; Jones, R.N. Dalbavancin activity against selected populations of antimicrobial-resistant Gram-positive pathogens. *Diagn. Microbiol. Infect. Dis.*, **2005**, *53*, 307-10.

[46]   Zhanel, G.G.; DeCorby, M.; Nichol, K.A.; Wierzbowski, A.; Baudry, P.J.; Karlowsky, J.A.; Lagacé-Wiens, P.; Walkty, A.; Mulvey, M.R.; Hoban, D.J. Antimicrobial susceptibility of 3931 organisms isolated from intensive care units in Canada: Canadian National Intensive Care Unit Study, 2005/2006. *Diagn. Microbiol. Infect. Dis.*, **2008**, *62*, 67-80.

[47]   Mushtaq, S.; Warner, M.; Johnson, A.P.; Livermore, D.M. Activity of dalbavancin against staphylococci and streptococci, assessed by BSAC and NCCLS agar dilution methods. *J. Antimicrob. Chemother.*, **2004**, *54*, 617-20.

[48]   Pace, J.L.; Yang, G. Glycopeptides: update on an old successful antibiotic class. *Biochem. Pharmacol.*, **2006**, *71*, 968-80.

[49]   Poeta, P.; Radhouani, H.; Sargo, R.; Igrejas, G. *In vitro* activity of dalbavancin against enterococci isolates from wild animals, pets, poultry and humans in Portugal. *J. Basic Microbiol.*, **2008**, *48*, 526-8.

[50]   Goldstein, B.P.; Draghi, D.C.; Sheehan, D.J.; Hogan, P.; Sahm, D.F. Bactericidal activity and resistance development profiling of dalbavancin. *Antimicrob. Agents Chemother.*, **2007**, *51*, 1150-4.

[51]   Lopez, S.; Hackbarth, C.; Romano, G.; Trias, J.; Jabes, D.; Goldstein, B.P. *In vitro* antistaphylococcal activity of dalbavancin, a novel glycopeptide. *J. Antimicrob. Chemother.*, **2005**, *55*(Suppl. S2), 221-224.

[52]   Lefort, A.; Pavie, J.; Garry, L.; Chau, F.; Fantin, B. Activities of dalbavancin *in vitro* and in a rabbit model of experimental endocarditis due to *Staphylococcus aureus* with or without reduced susceptibility to vancomycin and teicoplanin. *Antimicrob. Agents Chemother.*, **2004**, *48*, 1061-4.

[53]   Nicolau, D.P.; Sun, H.K.; Seltzer, E.; Buckwalter, M.; Dowell, J.A. Pharmacokinetics of dalbavancin in plasma and skin blister fluid. *J. Antimicrob. Chemother.*, **2007**, *60*, 681-4.

[54]   Anderson, V.R.; Keating, G.M. Dalbavancin. *Drugs*, **2008**, *68*, 639-48.

[55]   Buckwalter, M.; Dowell, J.A. Population pharmacokinetic analysis of dalbavancin, a novel lipoglycopeptide. *J. Clin. Pharmacol.*, **2005**, *45*, 1279-87.

[56]   Nord, C.E.; Rasmanis, G.; Wahlund, E. Effect of dalbavancin on the normal intestinal microflora. *J. Antimicrob. Chemother.*, **2006**, *58*, 627-31.

[57]   Raad, I.; Darouiche, R.; Vazquez, J.; Lentnek, A.; Hachem, R.; Hanna, H.; Goldstein, B.; Henkel, T.; Seltzer, E. Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens. *Clin. Infect. Dis.*, **2005**, *40*, 374-80.

[58]   Jauregui, L.E.; Babazadeh, S.; Seltzer, E.; Goldberg, L.; Krievins, D.; Frederick, M.; Krause, D.; Satilovs, I.; Endzinas, Z.; Breaux, J.; O'Riordan, W. 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

[59]   Leighton, A.; Gottlieb, A.B.; Dorr, M.B.; Jabes, D.; Mosconi, G.; VanSaders, C.; Mroszczak, E.J.; Campbell, K.C.M.; Kelly. E. Tolerability, pharmacokinetics, and serum bactericidal activity of intravenous dalbavancin in healthy volunteers. *Antimicrob. Agents Chemother.*, **2004**, *48*, 940-5.

[60]   Seltzer, E.; Dorr, M.B.; Goldstein, B.P.; Perry, M.; Dowell, J.A.; Henkel, T.; the Dalbavancin Skin and Soft-Tissue Infection Study Group. Once-weekly dalbavancin versus standard-of-care antimicrobial regimens for treatment of skin and soft-tissue infections. *Clin. Infect. Dis.*, **2003**, *37*, 1298-303.

[61]   Campbell, K.C.; Kelly, E.; Targovnik, N.; Hughes, L.; Van Saders, C.; Gottlieb, A.B.; Dorr, M.B.; Leighton, A. Audiologic monitoring for potential ototoxicity in a phase I clinical trial of a new glycopeptide antibiotic. *J. Am. Acad. Audiol.*, **2003**, *14*, 157-68.

[62]   Decousser, J.W.; Bourgeois-Nicolaos, N.; Doucet-Populaires, F. Dalbavancin, a long-acting lipoglycopeptide for the treatment of multidrug-resistant Gram-positive bacteria. *Expert. Rev. Anti. Infect. Ther.*, **2007**, *5*, 557-71.

[63]   Dunbar, L.M.; Tang, D.M.; Manausa, R.M. A review of telavancin in the treatment of complicated skin and skin structure infections (cSSSI). *Ther. Clin. Risk Manag.*, **2008**, *4*, 235-44.

[64]   Higgins, D.L.; Chang, R.; Debabov, D.V.; Leung, J.; Wu, T.; Krause, K.M.; Sandvik, E.; Hubbard, J.M.; Kaniga, K.; Schmidt, D.E.; Gao, Q.; Cass, R.T.; Karr, D.E.; Benton, B.M.; Humphrey, P.P. Telavancin, a multifunctional lipoglycopeptide, disrupts both cell wall synthesis and cell membrane integrity in methicillin-resistant *Staphylococcus aureus*. *Antimicrob. Agents Chemother.*, **2005**, *49*, 1127-34.

[65]   Leonard, S.N.; Rybak, M.J. Telavancin: an antimicrobial with a multifunctional mechanism of action for the treatment of serious gram-positive infections. *Pharmacotherapy*, **2008**, *28*, 458-68.

[66]   Micek, ST. Alternatives to vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. *Clin. Infect. Dis.*, **2007**, *45*, 184-90.

[67]   Drew, R.H. Emerging options for treatment of invasive, multidrug-resistant *Staphylococcus aureus* infections. *Pharmacotherapy*, **2007**, *27*, 227-49.

[68]   Draghi, D.C.; Benton, B.M.; Krause, K.M.; Thornsberry, C.; Pillar, C.; Sahm, D.F. Comparative surveillance study of telavancin activity against recently collected Gram-positive clinical isolates from across the United States. *Antimicrob. Agents Chemother.*, **2008**, *52*, 2383-8.

[69]   Draghi, D.C.; Benton, B.M.; Krause, K.M.; Thornsberry, C.; Pillar, C.; Sahm, D.F. *In vitro* activity of telavancin against recent Gram-positive clinical isolates: results of the 2004-05 Prospective European Surveillance Initiative. *J. Antimicrob. Chemother.*, **2008**, *62*, 116-21.

[70]   Gander, S.; Kinnaird, A.; Finch, R. Telavancin: *in vitro* activity against staphylococci in a biofilm model. *J. Antimicrob. Chemother.*, **2005**, *56*, 337-43.

[71]   Jansen, W.T.M.; Verel, A.; Verhoef, J.; Milatovic, D. *In vitro* activity of telavancin against Gram-positive clinical isolates recently obtained in Europe. *Antimicrob. Agents Chemother.*, **2007**, *51*, 3420-4.

[72]   King, A.; Phillips, I.; Kaniga, K. Comparative *in vitro* activity of telavancin (TD-6424), a rapidly bactericidal, concentration-dependent anti-infective with multiple mechanisms of action against Gram-positive bacteria. *J. Antimicrob. Chemother.*, **2004**, *53*, 797-803.

[73]   Krause, K.M.; Renelli, M.; Difuntorum, S.; Wu, T.X.; Debabov, D.V.; Benton, B.M. *In vitro* activity of telavancin against resistant gram-positive bacteria. *Antimicrob. Agents Chemother.*, **2008**, *52*, 2647-52.

[74]   Shaw, J.P.; Seroogy, J.; Kaniga, K.; Higgins, D.L.; Kitt, M.; Barriere, S. Pharmacokinetics, serum inhibitory and bactericidal activity, and safety of telavancin in healthy subjects. *Antimicrob. Agents Chemother.*, **2005**, *49*, 195-201.

[75]   Wong, S.L.; Barriere, S.L.; Kitt, M.M.; Goldberg, M.R. Multiple-dose pharmacokinetics of intravenous telavancin in healthy male and female subjects. *J. Antimicrob. Chemother.*, **2008**, *62*, 780-3.

[76]   Leuthner, K.D.; Cheung, C.M.; Rybak, M.J. Comparative activity of the new lipoglycopeptide telavancin in the presence and absence of serum against 50 glycopeptide nonsusceptible staphylococci and three vancomycin-resistant *Staphylococcus aureus*. *J. Antimicrob. Chemother.*, **2006**, *58*, 338-43.

[77]   Sun, H.K.; Duchin, K.; Nightingale, C.H.; Shaw, J.P.; Seroogy, J.; Nicolau, D.P. Tissue penetration of telavancin after intravenous administration in healthy subjects. *Antimicrob. Agents Chemother.*, **2006**, *50*, 788-90.

[78]   Gotfried, M.H.; Shaw, J.P.; Benton, B.M.; Krause, K.M.; Goldberg, M.R.; Kitt, M.M.; Barriere, S.L. Intrapulmonary distribution of intravenous telavancin in healthy subjects and effect of pulmonary surfactant on *in vitro* activities of telavancin and other antibiotics. *Antimicrob. Agents Chemother.*, **2008**, *52*, 92-7.

[79]   Stryjewski, M.E.; Graham, D.R.; Wilson, S.E.; O'Riordan, W.; Young, D.; Lentnek, A.; Ross, D.P.; Fowler, V.G.; Hopkins, A.; Friedland, H.D.; Barriere, S.L.; Kitt, M.M.; Corey, G.R. Telavancin versus vancomycin for the treatment of complicated skin and skin-structure infections caused by gram-positive organisms. *Clin. Infect. Dis.*, **2008**, *46*, 1683-93.

[80]   Stryjewski, M.E.; Chu, V.H.; O'Riordan, W.D.; Warren, B.L.; Dunbar, L.M.; Young, D.M.; Vallée, M.; Fowler, V.G.; Morganroth, J.; Barriere, S.L.; Kitt, M.M.; Corey, G.R. Telavancin versus standard therapy for treatment of complicated skin and skin structure infections caused by gram-positive bacteria: FAST 2 Study. *Antimicrob. Agents Chemother.*, **2006**, *50*, 862-7.

[81]   Barriere, S.; Genter, F.; Spencer, E.; Kitt, M.; Hoelscher, D.; Morganroth, J. Effects of a new antibacterial, telavancin, on cardiac repolarization (QTc interval duration) in healthy subjects. *J. Clin. Pharmacol.*, **2004**, *44*, 689-95.

[82]   Barcia-Macay, M.; Mouaden, F.; Mingeot-Leclercq, M.P.; Tulkens, P.M.; Van Bambeke, F. Cellular pharmacokinetics of telavancin, a novel lipoglycopeptide antibiotic, and analysis of lysosomal changes in cultured eukaryotic cells (J774 mouse macrophages and rat embryonic fibroblasts). *J. Antimicrob. Chemother.*, **2008**, *61*, 1288-94.

[83]   Barcia-Macay, M.; Lemaire, S.; Mingeot-Leclercq, M.P.; Tulkens, P.M.; Van Bambeke, F. Evaluation of the extracellular and intracellular activities (human THP-1 macrophages) of telavancin versus

[84]   Madrigal, A.G.; Basuino, L.; Chambers, H.F. Efficacy of telavancin in a rabbit model of aortic valve endocarditis due to methicillin-resistant *Staphylococcus aureus* or vancomycin-intermediate *Staphylococcus aureus*. *Antimicrob. Agents Chemother.*, **2005**, *49*, 3163-5.

[85]   Miró, J.M.; García-de-la-Maria, C.; Armero, Y.; de-Lazzari, E.; Soy, D.; Moreno, A.; del Rio, A., Almela, M.; Mestres, C.A.; Gatell, J.M.; Jiménez-de-Anta, M.T.; Marco, F; the Hospital Clínic Experimental Endocarditis Study Group. Efficacy of telavancin in the treatment of experimental endocarditis due to glycopeptide-intermediate *Staphylococcus aureus*. *Antimicrob. Agents Chemother.*, **2007**, *51*, 2373-7.

[86]   Clouse, F.L.; Hovde, L.B.; Rotschafer, J.C. *In vitro* evaluation of the activities of telavancin, cefazolin, and vancomycin against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* in peritoneal dialysate. *Antimicrob. Agents Chemother.*, **2007**, *51*, 4521-4.

[87]   Hegde, S.S.; Reyes, N.; Skinner, R.; Difuntorum, S. Efficacy of telavancin in a murine model of pneumonia induced by methicillin-susceptible *Staphylococcus aureus*. *J. Antimicrob. Chemother.*, **2008**, *61*, 169-72.

[88]   Reyes, N.; Skinner, R.; Kaniga, K.; Krause, K.M.; Shelton, J.; Obedencio, G.P.; Gough, A.; Conner, M.; Hegde, S.S. Efficacy of telavancin (TD-6424), a rapidly bactericidal lipoglycopeptide with multiple mechanisms of action, in a murine model of pneumonia induced by methicillin-resistant *Staphylococcus aureus*. *Antimicrob. Agents Chemother.*, **2005**, *49*, 4344-6.

[89]   Reyes, N.; Skinner, R.; Benton, B.M.; Krause, K.M.; Shelton, J.; Obedencio, G.P.; Hegde, S.S. Efficacy of telavancin in a murine model of bacteraemia induced by methicillin-resistant *Staphylococcus aureus*. *J. Antimicrob. Chemother.*, **2006**, *58*, 462-5.

[90]   Yin, L.Y.; Calhoun, J.H.; Thomas, T.S.; Wirtz, E.D. Efficacy of telavancin in the treatment of methicillin-resistant *Staphylococcus aureus* osteomyelitis: studies with a rabbit model. *J. Antimicrob. Chemother.*, **2009**, *63*, 357-60.

[91]   Stucki, A.; Gerber, P.; Acosta, F.; Cottagnoud, M.; Cottagnoud, P. Efficacy of telavancin against penicillin-resistant pneumococci and *Staphylococcus aureus* in a rabbit meningitis model and determination of kinetic parameters. *Antimicrob. Agents Chemother.*, **2006**, *50*, 770-3.

[92]   Allen, N.E.; Nicas, T.I. Mechanism of action of oritavancin and related glycopeptide antibiotics. *FEMS Microbiol. Rev.*, **2003**, *26*, 511-32.

[93]   Lentino, J.R.; Narita, M.; Yu, V.L. New antimicrobial agents as therapy for resistant gram-positive cocci. *Eur. J. Clin. Microbiol. Infect. Dis.*, **2008**, *27*, 3-15.

[94]   Cooper, R.D.; Snyder, N.J.; Zweifel, M.J.; Staszak, M.A.; Wilkie, S.C.; Nicas, T.I.; Mullen, D.L.; Butler, T.F.; Rodriguez, M.J.; Huff, B.E.; Thompson, R.C. Reductive alkylation of glycopeptide antibiotics: synthesis and antibacterial activity. *J. Antibiot. (Tokyo)*, **1996**, *49*, 575-81.

[95]   Belley, A.; Neesham-Grenon, E.; Mckay, G.; Arhin, F.F.; Harris, R.; Beveridge, T.; Parr, T.R.Jr.; Moeck, G. Oritavancin kills stationary-phase and biofilm *Staphylococcus aureus in vitro*. *Antimicrob. Agents Chemother.*, **2009**, *53*, 918-25.

[96]   Cabellos, C.; Fernandez, A.; Maiques, J.M.; Tubau, F.; Ardanuy, C.; Viladrich, P.F.; Linares, J.; Gudiol, F. Experimental study of LY333328 (oritavancin), alone and in combination, in therapy of cephalosporin-resistant pneumococcal meningitis. *Antimicrob. Agents Chemother.*, **2003**, *47*, 1907-11.

[97]   Citron, D.M.; Kwok, Y.Y.; Appleman, M.D. *In vitro* activity of oritavancin (LY333328), vancomycin, clindamycin, and metronidazole against *Clostridium perfringens*, *Propionibacterium acnes*, and anaerobic Gram-positive cocci. *Anaerobe*, **2005**, *11*, 93-5.

[98]   Crandon, J.; Nicolau, D.P. Oritavancin: a potential weapon in the battle against serious Gram-positive pathogens. *Future Microbiol.*, **2008**, *3*, 251-63.

[99]   Gosbell, I.B.; Fernandes, L.A.; Fernandes, C.J. *In vitro* antibacterial activity of beta-lactams and non-beta-lactams against *Streptococcus pneumoniae* isolates from Sydney, Australia. *Pathology*, **2006**, *38*, 343-8.

[100]   Noviello, S.; Ianniello, F.; Esposito, S. *In vitro* activity of LY333328 (oritavancin) against Gram-positive aerobic cocci and synergy with ciprofloxacin against enterococci. *J. Antimicrob. Chemother.*, **2001**, *48*, 283-6.

[101]   Zeckel, M.L.; Preston, D.A.; Allen, B.S. *In vitro* activities of LY333328 and comparative agents against nosocomial gram-positive pathogens collected in a 1997 global surveillance study. *Antimicrob. Agents Chemother.*, **2000**, *44*, 1370-4.

[102]   Heine, H.S.; Bassett, J.; Miller, L.; Bassett, A.; Ivins, B.E.; Lehoux, D.; Arhin, F.F.; Parr, T.R.Jr; Moeck, G. Efficacy of oritavancin in a murine model of *Bacillus anthracis* spore inhalation anthrax. *Antimicrob. Agents Chemother.*, **2008**, *52*, 3350-7.

[103]   Lefort, A.; Saleh-Mghir, A.; Garry, L.; Carbon, C.; Fantin, B. Activity of LY333328 combined with gentamicin *in vitro* and in rabbit experimental endocarditis due to vancomycin- susceptible or -resistant *Enterococcus faecalis. Antimicrob. Agents Chemother.*, **2000**, *44*, 3017-21.

[104]   Belley, A.; Neesham-Grenon, E.; Arhin, F.F.; McKay, G.A.; Parr, T.R.Jr; Moeck, G. Assessment by time-kill methodology of the synergistic effects of oritavancin in combination with other antimicrobial agents against *Staphylococcus aureus. Antimicrob. Agents Chemother.*, **2008**, *52*, 3820-2.

[105]   Baines, S.D.; O'Connor, R.; Saxton, K.; Freeman, J.; Wilcox, M.H. Comparison of oritavancin versus vancomycin as treatments for clindamycin-induced *Clostridium difficile* PCR ribotype 027 infection in a human gut model. *J. Antimicrob. Chemother.*, **2008**, *62*, 1078-85.

[106]   Bhavnani, S.M.; Owen, J.S.; Loutit, J.S.; Porter, S.B.; Ambrose, P.G. Pharmacokinetics, safety, and tolerability of ascending single intravenous doses of oritavancin administered to healthy human subjects. *Diagn. Microbiol. Infect. Dis.*, **2004**, *50*, 95-102.

[107]   Fetterly, G.J.; Ong, C.M.; Bhavnani, S.M., Loutit, J.S.; Porter, S.B.; Morello, L.G.; Ambrose, P.G.; Nicolau, D.P. Pharmacokinetics of oritavancin in plasma and skin blister fluid following administration of a 200-milligram dose for 3 days or a single 800-milligram dose. *Antimicrob. Agents Chemother.*, **2005**, *49*, 148-52.

[108]   Van Bambeke, F.; Saffran, J.; Mingeot-Leclercq, M.P.; Tulkens, P.M. Mixed-lipid storage disorder induced in macrophages and fibroblasts by oritavancin (LY333328), a new glycopeptide antibiotic with exceptional cellular accumulation. *Antimicrob. Agents Chemother.*, **2005**, *49*, 1695-700.

[109]   Sharpe, J.N. Antibiotics as an adjunct to surgical management of lower extremity ulcerations. *Microsurgery*, **2004**, *24*, 8-17.

[110]   Bogdanovich, T.; Clark, C.; Ednie, L.; Lin, G.; Smith, K.; Shapiro, S.; Appelbaum, P.C. Activities of ceftobiprole, a novel broad-spectrum cephalosporin, against *Haemophilus influenzae* and *Moraxella catarrhalis. Antimicrob. Agents Chemother.*, **2006**, *50*, 2050-7.

[111]   Deshpande, L.; Rhomberg, P.R.; Fritsche, T.R.; Sader, H.S. ; Jones, R.N. Bactericidal activity of BAL9141, a novel parenteral cephalosporin against contemporary Gram-positive and Gram-negative isolates. *Diagn. Microbiol. Infect. Dis.*, **2004**, *50*, 73-5.

[112]   Kosowska, K.; Hoellman, D.B.; Lin, G.; Clark, C.; Credito, K.; McGhee, P.; Dewasse, B.; Bozdogan, B.; Shapiro, S.; Appelbaum, P.C. Antipneumococcal activity of ceftobiprole, a novel broad-spectrum cephalosporin. *Antimicrob. Agents Chemother.*, **2005**, *49*, 1932-42.

[113]   Deresinski, S.C. Ceftobiprole: breaking therapeutic dogmas of the beta-lactam class. *Diagn. Microbiol. Infect. Dis.*, **2008**, *61*, 82-5.

[114]   Queenan, A.M.; Shang, W.; Kania, M.; Page, M.G.; Bush, K. Interactions of ceftobiprole with beta-lactamases from molecular classes A to D. *Antimicrob. Agents Chemother.*, **2007**, *51*, 3089-95.

[115]   Davies, T.A.; Shang, W.; Bush, K. Activities of ceftobiprole and other beta-lactams against *Streptococcus pneumoniae* clinical isolates from the United States with defined substitutions in penicillin-binding proteins PBP 1a, PBP 2b, and PBP 2x. *Antimicrob. Agents Chemother.*, **2006**, *50*, 2530-2.

[116]   Davies, T.A.; Page, M.G.; Shang, W.; Andrew, T.; Kania, M.; Bush, K. Binding of ceftobiprole and comparators to the penicillin-binding proteins of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pneumoniae. Antimicrob. Agents Chemother.*, **2007**, *51*, 2621-4.

[117]   Jones, M.E. In-vitro profile of a new beta-lactam, ceftobiprole, with activity against methicillin-resistant *Staphylococcus aureus. Clin. Microbiol. Infect.*, **2007**, *13*(Suppl 2), 17-24.

[118]   Noel, G.J. Clinical profile of ceftobiprole, a novel beta-lactam antibiotic. *Clin. Microbiol. Infect.*, 2007, *13*(Suppl 2), 25-9.

[119]   Page, M.G.P. Anti-MRSA betalactams in development. *Curr. Opin. Pharmacol.*, **2006**, *6*, 480-5.

[120]   Chambers, H.F. Ceftobiprole: in-vivo profile of a bactericidal cephalosporin. *Clin. Microbiol. Infect.*, **2006**, *12*(Suppl 2), 17-22.

[121]   Leonard, S.N.; Cheung, C.M., Rybak, M.J. Activities of ceftobiprole, linezolid, vancomycin, and daptomycin against community-associated and hospital-associated methicillin-resistant *Staphylococcus aureus. Antimicrob. Agents Chemother.*, **2008**, *52*, 2974-6.

[122]   Amsler, K.M.; Davies, T.A.; Shang, W.; Jacobs, M.R.; Bush, K. *In vitro* activity of ceftobiprole against pathogens from two phase 3 clinical trials of complicated skin and skin structure infections. *Antimicrob. Agents Chemother.*, **2008**, *52*, 3418-23.

[123]   Anderson, S.D.; Gums, J.G. Ceftobiprole: an extended-spectrum anti-methicillin-resistant *Staphylococcus aureus* cephalosporin. *Ann. Pharmacother.*, **2008**, *42*, 806-16.

[124]   Bogdanovich, T.; Ednie, L.M.; Shapiro, S., Appelbaum, P.C. Antistaphylococcal activity of ceftobiprole, a new broad-spectrum cephalosporin. *Antimicrob. Agents Chemother.*, **2005**, *49*, 4210-9.

[125]   Chung, M.; Antignac, A.; Kim, C.; Tomasz, A. Comparative study of the susceptibilities of major epidemic clones of methicillin-resistant *Staphylococcus aureus* to oxacillin and to the new broad-spectrum cephalosporin ceftobiprole. *Antimicrob. Agents Chemother.*, **2008**, *52*, 2709-17.

[126]   Denis, O.; Deplano, A.; Nonhoff, C.; Hallin, M.; De Ryck, R.; Vanhoof, R.; De Mendonca, R., Struelens, M.J. *In vitro* activities of ceftobiprole, tigecycline, daptomycin, and 19 other antimicrobials against methicillin-resistant *Staphylococcus aureus* strains from a national survey of Belgian hospitals. *Antimicrob. Agents Chemother.*, **2006**, *50*, 2680-5.

[127]   Drees, M.; Boucher, H. New agents for *Staphylococcus aureus* endocarditis. *Curr. Opin. Infect. Dis.*, **2006**, *19*, 544-50.

[128]   Fritsche, T.R.; Sader, H.S.; Jones, R.N. 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.

[129]   Goldstein, E.J.C.; Citron, D.M.; Merriam, C.V.; Warren, Y.A.; Tyrrell, K.L.; Fernandez, H.T. *In vitro* activity of ceftobiprole against aerobic and anaerobic strains isolated from diabetic foot infections. *Antimicrob. Agents Chemother.*, **2006**, *50*, 3959-62.

[130]   Issa, N.C.; Rouse, M.S.; Piper, K.E.; Wilson, W.R.; Steckelberg, J.M.; Patel, R. *In vitro* activity of BAL9141 against clinical isolates of gram-negative bacteria. *Diagn. Microbiol. Infect. Dis.*, **2004**, *48*, 73-5.

[131]   Jones, R.N.; Deshpande, L.M.; Mutnick, A.H.; Biedenbach, D.J. *In vitro* evaluation of BAL9141, a novel parenteral cephalosporin active against oxacillin-resistant staphylococci. *J. Antimicrob. Chemother.*, **2002**, *50*, 915-32.

[132]   Pillar, C.M.; Aranza, M.K.; Shah, D.; Sahm, D.F. *In vitro* activity profile of ceftobiprole, an anti-MRSA cephalosporin, against recent gram-positive and gram-negative isolates of European origin. *J. Antimicrob. Chemother.*, **2008**, *61*, 595-602.

[133]   Rossolini, G.M. Redesigning beta-lactams to combat resistance: summary and conclusions. *Clin. Microbiol. Infect.*, **2007**, *13*(Suppl 2), 30-3.

[134]   Wang, H.; Liu, Y.; Sun, H.; Xu, Y.; Xie, X.; Chen, M. *In vitro* activity of ceftobiprole, linezolid, tigecycline, and 23 other antimicrobial agents against *Staphylococcus aureus* isolates in China. *Diagn. Microbiol. Infect. Dis.*, **2008**, *62*, 226-9.

[135]   Zhanel, G.G.; Lam, A.; Schweizer, F.; Thomson, K.; Walkty, A.; Rubinstein, E.; Gin, A.S.; Hoban, D.J.; Noreddin, A.M.; Karlowxky, J.A. Ceftobiprole: a review of a broad-spectrum and anti-MRSA cephalosporin. *Am. J. Clin. Dermatol,*, **2008**, *9*, 245-54.

[136]   Walkty, A.; Decorby, M.; Nichol, K.; Karlowsky, J.A.; Hoban, D.J.; Zhanel, G.G. *In vitro* activity of ceftobiprole against clinical isolates of *Pseudomonas aeruginosa* obtained from Canadian intensive care unit (ICU) patients as part of the CAN-ICU Study. *J. Antimicrob. Chemother.*, **2008**, *62*, 206-8.

[137]   Zbinden, R.; Pünter, V.; von Graevenitz, A. *In vitro* activities of BAL9141, a novel broad-spectrum pyrrolidinone cephalosporin, against Gram-negative nonfermenters. *Antimicrob. Agents Chemother.*, **2002**, *46*, 871-4.

[138]   Ednie, L.; Shapiro, S.; Appelbaum, P.C. Antianaerobe activity of ceftobiprole, a new broad-spectrum cephalosporin. *Diagn. Microbiol. Infect. Dis.*, **2007**, *58*, 133-6.

[139]   Wootton, M.; Bowker, K.E.; Holt, H.A.; MacGowan, A.P. BAL 9141, a new broad-spectrum pyrrolidinone cephalosporin: activity against clinically significant anaerobes in comparison with 10 other antimicrobials. *J. Antimicrob. Chemother.*, **2002**, *49*, 535-9.

[140]   Banerjee, R.; Gretes, M.; Basuino, L.; Strynadka, N.; Chambers, H.F. *In vitro* selection and characterization of ceftobiprole-resistant methicillin-resistant *Staphylococcus aureus*. *Antimicrob. Agents Chemother.*, **2008**, *52*, 2089-96.

[141]   Murthy, B.; Schmitt-Hoffmann, A. Pharmacokinetics and pharmacodynamics of ceftobiprole, an anti-MRSA cephalosporin with broad-spectrum activity. *Clin. Pharmacokinet.*, **2008**, *47*, 21-33.

[142]   Schmitt-Hoffmann, A.; Roos, B.; Schleimer, M.; Sauer, J.; Man, A.; Nashed, N.; Brown, T.; Perez, A.; Weidekamm, E.; Kovács, P. Single-dose pharmacokinetics and safety of a novel broad-spectrum cephalosporin (BAL5788) in healthy volunteers. *Antimicrob. Agents Chemother.*, **2004**, *48*, 2570-5.

[143]   Schmitt-Hoffmann, A.; Nyman, L.; Roos, B.; Schleimer, M.; Sauer, J.; Nashed, N.; Brown, T.; Man, A.; Weidekamm, E. Multiple-dose pharmacokinetics and safety of a novel broad-spectrum cephalosporin (BAL5788) in healthy volunteers. *Antimicrob. Agents Chemother.*, **2004**, *48*, 2576-80.

[144]   Noel, G.J.; Bush, K.; Bagchi, P.; Ianus, J.; Strauss, R.S. A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. *Clin. Infect. Dis.*, **2008**, *46*, 647-55.

[145]   Entenza, J.M.; Hohl, P.; Heinze-Krauss, I.; Glauser, M.P.; Moreillon, P. BAL9141, a novel extended-spectrum cephalosporin active against methicillin-resistant *Staphylococcus aureus* in treatment of experimental endocarditis. *Antimicrob. Agents Chemother.*, **2002**, *46*, 171-7.

[146]   Rouse, M.S.; Hein, M.M.; Anguita-Alonso, P.; Steckelberg, J.M.; Patel, R. Ceftobiprole medocaril (BAL5788) treatment of experimental *Haemophilus influenzae*, *Enterobacter cloacae*, and *Klebsiella pneumoniae* murine pneumonia. *Diagn. Microbiol. Infect. Dis.*, **2006**, *55*, 333-6.

[147]   Arias, C.A.; Singh, K.V.; Panesso, D.; Murray, B.E. Time-kill and synergism studies of ceftobiprole against *Enterococcus faecalis*, including beta-lactamase-producing and vancomycin-resistant isolates. *Antimicrob. Agents Chemother.*, **2007**, *51*, 2043-7.

[148]   Laue, H.; Weiss, L.; Bernardi, A.; Hawser, S.; Lociuro, S.; Islam, K. *In vitro* activity of the novel diaminopyrimidine, iclaprim, in combination with folate inhibitors and other antimicrobials with different mechanisms of action. *J. Antimicrob. Chemother.*, **2007**, *60*, 1391-4.

[149]   Schneider, P.; Hawser, S.; Islam, K. Iclaprim, a novel diaminopyrimidine with potent activity on trimethoprim sensitive and resistant bacteria. *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 4217-21.

[150]   Zhanel, G.G.; Karlowsky, J.A. *In vitro* activity of iclaprim against respiratory and bacteremic isolates of *Streptococcus pneumoniae*. *Antimicrob. Agents Chemother.*, **2009**, *53*, 1690-2.

[151]   Kohlhoff, S.A.; Roblin, P.M.; Reznik, T.; Hawser, S.; Islam, K.; Hammerschlag, M.R. *In vitro* activity of a novel diaminopyrimidine compound, iclaprim, against *Chlamydia trachomatis* and *Chlamydia pneumoniae*. *Antimicrob. Agents Chemother.*, **2004**, *48*, 1885-6.

[152]   Bozdogan, B.; Esel, D.; Whitener, C.; Browne, F.A.; Appelbaum, P.C. Antibacterial susceptibility of a vancomycin-resistant *Staphylococcus aureus* strain isolated at the Hershey Medical Center. *J. Antimicrob. Chemother.*, **2003**, *52*, 864-8.

[153]   Kohlhoff, S.A.; Sharma, R. Iclaprim. *Expert. Opin. Investig. Drugs*, **2007**, *16*, 1441-8.

[154]   Morrissey, I.; Maher, K.; Hawser, S. Activity of iclaprim against clinical isolates of *Streptococcus pyogenes* and *Streptococcus agalactiae*. *J. Antimicrob. Chemother.*, **2009**, *63*, 413-4.

[155]   Morrissey, I.; Hawser, S. Activity of iclaprim against *Legionella pneumophila*. *J. Antimicrob. Chemother.*, **2007**, *60*, 905-6.

[156]   Andrews, J.; Honeybourne, D.; Ashby, J.; Jevons, G.; Fraise, A.; Fry, P.; Warrington, S.; Hawser, S.; Wise, R. 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.

[157]   French, G.L. What's new and not so new on the antimicrobial horizon? *Clin. Microbiol. Infect.*, **2008**, *14*(Suppl 6), 19-29.

[158]   Peppard, W.J.; Schuenke, D.C. Iclaprim, a diaminopyrimidine dihydrofolate reductase inhibitor for the potential treatment of antibiotic-resistant staphylococcal infections. *Curr. Opin. Investig. Drugs*, **2008**, *9*, 210-25.