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Oritavancin: A Review in Acute Bacterial Skin and Skin Structure Infections

Yahiya Y. Syed[1] · **Lesley J. Scott**[1]

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Abstract Oritavancin (Orbactiv®) is a new generation lipoglycopeptide approved for use in adult patients with acute bacterial skin and skin structure infections (ABSSSI). It is administered as a single 1200 mg intravenous infusion over 3 h. In phase 3 trials in adult patients with ABSSSI, oritavancin was noninferior to vancomycin in terms of a composite outcome (cessation of spreading or reduction in the size of the baseline lesion, absence of fever and no rescue antibacterials required; primary endpoint) assessed at an US FDA-recommended early timepoint of 48–72 h after initiation of treatment. Oritavancin was also noninferior to vancomycin in terms of a ≥20 % reduction in the baseline lesion size at the early timepoint and clinical cure rate 7–14 days after the end of treatment. Oritavancin was generally well tolerated in the phase 3 trials, with most treatment-emergent adverse reactions being mild in severity. The most common adverse events occurring in oritavancin recipients were nausea, headache, vomiting, limb and subcutaneous abscesses, and diarrhoea. Oritavancin offers a number of potential advantages, including a convenient single dose treatment that may shorten or eliminate hospital stays, a reduction in healthcare resource utilization and cost, no need for dosage adjustment in patients with mild to moderate hepatic or renal impairment, no need for therapeutic drug monitoring, and elimination of compliance concerns. Therefore, oritavancin is a useful treatment option for adults with ABSSSI.

Oritavancin: clinical considerations in acute bacterial skin and skin structure infections

New generation lipoglycopeptide with potent in vitro activity against Gram-positive bacteria causing ABSSSI, including methicillin-resistant *Staphylococcus aureus*, streptococci and enterococci

At least three mechanisms of action, which contribute to rapid and concentration-dependent bactericidal activity

Low potential for the emergence of oritavancin-resistant strains

Noninferior to vancomycin for a composite clinical outcome (primary endpoint) and a ≥20 % reduction in the baseline lesion size 48–72 h after initiation of treatment, and for clinical cure rate 7–14 days after the end of treatment

Generally well tolerated

Convenient single dose treatment, without a need for dosage adjustment or therapeutic drug monitoring

The manuscript was reviewed by: ***N. E. Holmes***, Department of Infectious Diseases, Austin Health, Heidelberg, Australia; ***R. N. Jones,*** JMI Laboratories, North Liberty, IA, USA; ***B. M. Lomaestro***, Department of Pharmacy, Albany Medical Center Hospital, Albany, NY, USA; ***C. V. Pollack***, Department of Emergency Medicine, Thomas Jefferson University, Philadelphia, PA, USA; ***K. A. Rodvold***, Colleges of Pharmacy and Medicine, University of Illinois at Chicago, Chicago, IL, USA; ***F. Van Bambeke***, Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium.

✉ Yahiya Y. Syed
demail@springer.com

[1] Springer, Private Bag 65901, Mairangi Bay, 0754 Auckland, New Zealand

1 Introduction

The US FDA defines acute bacterial skin and skin structure infections (ABSSSI; previously known as complicated skin and skin structure infections) as bacterial infections of the skin with a lesion size area of ≥75 cm^2 (measured by the area of redness, oedema or induration) and includes wound infection, cellulitis/erysipelas and major cutaneous abscess [1]. ABSSSI are typically caused by Gram-positive bacteria, most commonly *Staphylococcus aureus* [including methicillin-resistant *S. aureus* (MRSA)] and *Streptococcus pyogenes* [1]. Other Gram-positive (other *Streptococcus* species and *Enterococcus* species), Gram-negative and anaerobic bacteria, and polymicrobial infections may also be present in ABSSSI [2].

ABSSSI are associated with a substantial economic burden because of high hospitalization rates and antibacterial therapy with agents that typically require once- to thrice-daily administration for 5–14 days [3–5]. In order to achieve good clinical outcomes at minimal cost with these regimens, patient care needs to be transitioned through multiple treatment settings (often including outpatient parenteral antimicrobial therapy), using complex strategies and planning [3]. However, outpatient treatment may not overcome the shortcomings of multiple drug administrations, complex therapeutic drug monitoring, dosage adjustments, patient inconvenience caused by the use of peripherally inserted central catheters, and poor compliance [3, 6]. Longer-acting antibacterials with reduced administration frequency may mitigate some of these problems [3].

The naturally occurring glycopeptides vancomycin and teicoplanin (a first generation lipoglycopeptide; not approved in the USA) have been key parenteral antibacterials used against Gram-positive infections, particularly MRSA [7]. However, the emergence of bacterial strains resistant to these agents is associated with an increasing incidence of treatment failures and worsening clinical outcomes. The most problematic resistant strains are vancomycin-intermediate *S. aureus* (VISA), heterogeneous VISA (hVISA), vancomycin-resistant *S. aureus* (VRSA) and vancomycin-resistant enterococci (VRE). Therefore, second generation semisynthetic lipoglycopeptides (e.g. oritavancin), which have a low potential for evolution of resistance, have been developed. Furthermore, these agents are more potent and longer acting than vancomycin, and thus, permit less frequent administrations [7].

Intravenous oritavancin (Orbactiv®) is the first single-dose antibacterial therapy to be approved in the USA [8] and EU [9] for the treatment of adult patients with ABSSSI. This narrative review focuses on the clinical efficacy and tolerability of oritavancin in these patients, and provides an overview of its pharmacological properties.

2 Pharmacodynamic Properties of Oritavancin

2.1 Mechanism of Action

Oritavancin is a vancomycin analogue derived from chloroeremomycin, from which it differs by the addition of a lipophilic N-4-(4-chlorophenyl)benzyl side chain [10]. It has multiple mechanisms of action which contribute to its concentration-dependent bactericidal activity. Oritavancin inhibits cell wall synthesis by inhibiting the transglycosylation (polymerization) and transpeptidation (crosslinking) steps by binding to the carboxyl terminal acyl-D-alanyl-D-alanine residues of the stem pentapeptide in nascent peptidoglycan chain and peptidic crosslinking segments, respectively. Unlike other glycopeptides, oritavancin is able to bind to depsipeptides, including D-alanyl-D-lactate residues, which are present in organisms exhibiting VanA-type resistance [10]. Additionally, oritavancin disrupts cell membrane integrity, resulting in depolarization, increased permeability and rapid cell death [10, 11]; an ultrastructural study revealed that oritavancin caused septal distortions in MRSA and VRE [12]. The lipophilic side chain anchors the drug to the cell membrane and thus, enhances its affinity for the target site [10].

2.2 Antibacterial Activity

2.2.1 In Vitro Activity

This section mainly focuses on the antibacterial activity of oritavancin against Gram-positive bacteria causing ABSSSI as specified in the US manufacturer's prescribing information (Table 1) [8]. In surveillance studies discussed, clinical isolates were collected between 2005 and 2014 in the USA and/or Europe [13–20], USA, Europe and Asia [21–26], Canada [27] or worldwide [28]. Most studies were conducted as part of the SENTRY Antimicrobial Surveillance programme [14, 15, 17, 18, 20–25, 28]. In all studies, the minimum inhibitory concentration (MIC) required to inhibit the growth of 90 % of isolates (MIC_{90}) was determined using broth microdilution techniques, with the addition of polysorbate 80 to testing media. Susceptibility to oritavancin was based on the US FDA breakpoints (Table 1). As with glycopeptide antibacterials in general, oritavancin has no intrinsic activity against Gram-negative bacteria [9].

Oritavancin showed potent in vitro activity against the target pathogens, with MIC_{90} values several-fold lower than those of vancomycin, and where reported, ≥98 % of clinical isolates were susceptible to oritavancin and all isolates were susceptible to vancomycin (Table 1). At least 90 % of vancomycin-susceptible *Enterococcus faecium* demonstrated an in vitro MIC of ≤0.12 μg/mL (the susceptibility

Table 1 In vitro activity of oritavancin compared with vancomycin against targeted Gram-positive clinical isolates specified in the US manufacturer's prescribing information

Species	No. of isolates[a]	ORI		VAN		References
		MIC_{90} (μg/mL)	Susceptible isolates (%)[b]	MIC_{90}	Susceptible isolates (%)[c]	
Staphylococcus aureus	3004–17,717	0.06–0.12		1	100/100	[13, 14, 20, 23, 24, 26]
MRSA	124–4882	0.06–0.12	98.4–99.5	1	100/100	[13, 15–17, 19, 20, 23–27]
MSSA	523–7127	0.06–0.12	99.2–99.7	1	100/100	[13, 15, 17, 19, 23–27]
Streptococcus pyogenes	55–959	0.12–0.25	98.4–99.2	0.25–0.5	100/100	[15, 16, 19, 23, 24, 26, 27]
Streptococcus agalactiae	55–415	0.06–0.25	97.9–100	0.5	100/100	[15, 16, 19, 23, 24, 26, 27]
Streptococcus dysgalactiae	22–59	0.25–0.5	98.3–100	0.25–0.5	–/100	[13, 24]
Streptococcus anginosus group	78–194	≤0.008–0.015	100	1	100/100	[3, 13, 24, 28]
S. anginosus	128	≤0.008				[28]
Enterococcus faecalis (VAN-S)	1311–1919	0.03–0.06	99.5	2	100/100	[17, 18, 21, 24, 26]

EUCAST European Committee on Antimicrobial Susceptibility Testing, *MIC_{90}* minimum inhibitory concentration (MIC) required to inhibit the growth of 90 % of isolates, *MRSA* methicillin-resistant *S. aureus*, *MSSA* methicillin-susceptible *S. aureus*, *ORI* oritavancin, *PK/PD* pharmacokinetic/pharmacodynamic; *VAN* vancomycin, *VAN-S* VAN-susceptible

[a] Not reported in one study [24]

[b] Using US FDA breakpoints: ≤0.12 μg/mL for *S. aureus* (including MRSA) and *E. faecalis* (VAN-S only), and ≤0.25 μg/mL for all other species [8]. The EUCAST breakpoints indicating susceptibility and resistance to oritavancin are: ≤0.125 and >0.125 mg/L for *S. aureus*; ≤0.25 and >0.25 mg/L for streptococci (groups A, B, C, G) and for *S. anginosus* group. Based on the PK/PD target for *S. aureus*, the susceptibility and resistant breakpoints for oritavancin were ≤0.125 and >0.125 mg/L; the PK/PD target for *S. pyogenes* is uncertain [73]

[c] Using Clinical and Laboratory Standards Institute/EUCAST breakpoints

breakpoint for vancomycin-susceptible *Enterococcus faecalis*) for oritavancin; however, the efficacy and safety of oritavancin in treating clinical infections caused by this species is not established in adequate well-controlled clinical trials [8]. Oritavancin MIC_{90} values for MRSA did not differ between clinical isolates collected in the USA and Europe, with the differences within twofold for *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *S. pyogenes* and *Streptococcus anginosus* group [15, 19, 20]. In phase 3 trials (Sect. 4), oritavancin MIC_{90} values against MRSA and methicillin-susceptible *S. aureus* (MSSA) isolates (0.12 μg/mL for both; $n = 404$ and 535) [13] were consistent with those in the surveillance studies (Table 1).

The in vitro activity of oritavancin has been tested against clinical isolates with reduced susceptibility to vancomycin and other drugs. The MIC_{90} value for oritavancin was ≤0.12 μg/mL against multidrug-resistant (MDR) *S. aureus* strains (susceptibility ≥98 %; $n = 337$–1345) [20, 22, 25, 27], MRSA strains with a vancomycin MIC of 2 μg/mL ($n = 124$) [17] and *S. aureus* strains with a vancomycin MIC of 2 μg/mL ($n = 205$) or a daptomycin MIC of 1–4 μg/mL ($n = 100$) [20]. MIC_{90} values for oritavancin against VRSA ($n = 10$), hVISA ($n = 11$) and VISA ($n = 14$) were 0.5, 1 and 2 μg/mL, respectively [29]. Oritavancin MIC_{90} values did not change between erythromycin-susceptible and -nonsusceptible strains of *S. agalactiae* and *S. pyogenes* [26] or between MDR and non-MDR strains of β-haemolytic and viridans streptococci [30]. Against vancomycin-resistant *E. faecalis*, oritavancin exhibited good in vitro activity against VanB-type (MIC_{90} 0.03 or 0.06 μg/mL; $n = 19$ and 17) as well as VanA-type (MIC_{90} 0.5–1 μg/mL; $n = 20$–65) strains [17, 18, 21, 24, 26]. Of note, oritavancin was more potent than dalbavancin against *E. faecalis* ($n = 14$) and *E. faecium* ($n = 15$) strains exhibiting VanA-type resistance (MIC_{90} ≤0.5 vs. >16 μg/mL; abstract presentation) [31]. Oritavancin had good in vitro activity against *S. aureus*, *E. faecalis* and *E. faecium* (MIC_{90} values 0.06, 0.12 and 0.12 μg/mL, respectively; $n = 25$, 13, 32) strains with elevated linezolid MICs [32].

Oritavancin had a MIC_{90} value of 0.06 μg/mL against MRSA isolates ($n = 14$) harbouring a novel gene, *mec*C, which was within a doubling dilution of its MIC_{90} value against isolates carrying the typical *mec*A gene, which confers methicillin resistance [33]. Oritavancin also showed good in vitro activity (MIC_{90} 0.25 μg/mL) against community-acquired MRSA isolates ($n = 58$), regardless of their genetic markers (presence or absence of Panton-Valentine leukocidin gene or presence of staphylococcal chromosome cassette *mec* type II or IV) [34].

2.2.2 Bactericidal Activity

In time-kill analyses, oritavancin at physiologically relevant concentrations demonstrated rapid, concentration-dependent bactericidal activity against Gram-positive

pathogens associated with ABSSSI [33, 35–42]. For example, oritavancin at 16 μg/mL was bactericidal [i.e. ≥3 $\log_{10}$ reductions in colony-forming unit (CFU)/mL from baseline] against MSSA, MRSA and VRSA (within 2 h), VISA (within 24 h), vancomycin-susceptible *E. faecalis* (within 6 h), and VRE (within 6 and 24 h against VanB and VanA strains); in comparison, vancomycin was bactericidal against MSSA and MRSA at 24 h [36]. Oritavancin showed bactericidal activity against a daptomycin-nonsusceptible MRSA strain (within 8 h) [39], exponentially-growing as well as stationary-phase and biofilm-producing *S. aureus* [36, 38], intracellular *S. aureus* [43], and *S. pyogenes*, including erythromycin-resistant strains (within 0.25–3 h) [35]. A simulated single oritavancin dose of 1200 mg produced significantly ($p < 0.05$) lower area under the bacterial-kill curve at 24 h than vancomycin 1000 mg twice daily against three MRSA strains [40]. Preliminary results (abstract presentations) suggest that oritavancin may be more potent than dalbavancin against MRSA (including non-dividing) isolates, with respect to the rate and/or extent of killing [41, 42, 44].

In time-kill assays, oritavancin showed synergistic activity with gentamicin or linezolid against MRSA (comprising VISA and hVISA strains) [37], VISA [45] and VRSA [45], with rifampin against 7 of 9 MRSA strains [37] and VRSA [45], and with gentamicin, moxifloxacin or rifampin against MSSA [45]. In vitro, there was no antagonism between oritavancin and gentamicin, moxifloxacin, linezolid or rifampin [8, 37].

2.3 Resistance Issues

There was no evidence for the emergence of bacterial resistance to oritavancin in surveillance (Table 1) or clinical studies [8]. In surveillance studies, including a longitudinal analysis [46], MIC_{90} values and susceptibility rates against specified bacteria have generally remained constant for oritavancin over the past several years. In vitro, emergence of *S. aureus* and *E. faecalis* strains resistant to oritavancin has been seen in serial passage studies [8]. The mechanism of resistance to oritavancin is not fully understood [10].

2.4 Pharmacokinetic/Pharmacodynamic Considerations

The oritavancin area under the plasma concentration–time curve (AUC) from time zero to 72 h (AUC_{72h}) to MIC_{90} ratio correlated well with its efficacy in phase 3 trials (abstract presentation) [47]. The AUC_{72h}:MIC_{90} ratio threshold for achieving post-therapy clinical cure (defined in Table 2) was determined to be 11,982 in patients with *S. aureus* infections, with 82.6 and 96.2 % of patients with AUC_{72h}:MIC_{90} ratios below and above this target, respectively, achieving clinical success ($p = 0.03$ for between-group comparison). The mean overall model-predicted probability of achieving clinical success was 95.4 % across oritavancin MIC values of 0.06–0.5 μg/mL against *S. aureus* [47].

2.5 In Vivo Activity

Consistent with its in vitro activity, oritavancin exhibited potent bactericidal effects in animal models of infection with *S. aureus* (including MRSA and MSSA), *E. faecalis* [vancomycin-susceptible and -resistant (both VanA- and VanB-type) strains] or *E. faecium* (VanA-type) [48, 49]. For example, a single human-equivalent dose of 1200 mg reduced MSSA or MRSA counts from baseline by ≥2.7 $\log_{10}$ CFU/thigh in a neutropenic murine thigh infection model [49]. The single-dose regimen was significantly ($p < 0.05$) more effective than daily regimens in this model [48, 49]. Subsequently, single-dose regimens were evaluated in a phase 2 study (Sect. 4).

3 Pharmacokinetic Properties of Oritavancin

The pharmacokinetics of oritavancin are linear at doses of up to 1200 mg [8] and are best described using a three-compartment model (α and β distributional phases followed by a terminal elimination phase), with zero-order intravenous infusion and first-order linear elimination [50, 51].

In a population pharmacokinetic analysis [51] of the phase 3 trials (which used the approved oritavancin dose of a single intravenous infusion of 1200 mg in patients with ABSSSI; Sect. 4), the model-derived mean maximum plasma concentration was 138 μg/mL and AUC_{72h} was 1530 μg · h/mL. AUC_{72h} is the main AUC parameter of interest for oritavancin (Sect. 2.4) and was consistent with the timing of the assessment of early clinical outcomes (i.e. 48–72 h after the start of therapy) in the phase 3 trials.

Oritavancin is highly (≈85 %) bound to human plasma proteins [8] and is extensively distributed into tissues (estimated total and mean steady-state volume of distribution 87.6 and 97.8 L) [8, 51]. Oritavancin showed modest penetration into cantharide-induced skin blister fluid in healthy volunteers; after a single intravenous infusion of 800 mg, the ratio of mean area under the blister fluid concentration–time curve at 24 h to that of plasma was 0.185; however, mean oritavancin concentrations in blister fluid exceeded its MIC_{90} value against *S. aureus* [52].

Nonclinical studies show that oritavancin is not metabolized [8]. In humans, unchanged oritavancin is slowly excreted in urine and faeces (<5 and <1 %, respectively, over 14 days) [8]. In patients with ABSSSI, oritavancin had a prolonged terminal elimination half-life (245 h), with

Table 2 Comparative efficacy of intravenous oritavancin in adult patients with acute bacterial skin and skin structure infections in double-blind, multinational, phase 3 noninferiority trials

Study or subgroup	No. of pts ORI/VAN[a]	Early clinical evaluation[b] (% pts)						Post-therapy clinical cure rate[c] (% pts)		
		Composite outcome[d]			≥20 % lesion size reduction					
		ORI	VAN	Difference (95 % CI)	ORI	VAN	Difference (95 % CI)	ORI	VAN	Difference (95 % CI)
SOLO I [6]	475/479[e]	82.3[f]	78.9[f]	3.4 (−1.6 to 8.4)[g]	86.9	82.9	4.1 (−0.5 to 8.6)[g]	79.6	80.0	−0.4 (−5.5 to 4.7)[g]
SOLO II [54]	503/502[e]	80.1[f]	82.9[f]	−2.7 (−7.5 to 2.0)[g]	85.9	85.3	0.6 (−3.7 to 5.0)[g]	82.7	80.5	2.2 (−2.6 to 7.0)[g]
Combined analyses										
All SOLO pts [57][h]	978/981[e]	81.2	80.9		86.4	84.1		81.2	80.2	
Outpatients only [56][h]	391/396	80.6	78.3		87.0	84.3		83.9	81.8	
By infection type [61][h]										
Wound infection	283/281	88.0	85.1		85.9	82.6		83.4	78.3	
Cellulitis	387/400	76.0	75.5		82.7	80.0		76.0	78.8	
Major cutaneous abscess	308/300	81.5	84.3		91.6	91.0		85.7	84.0	
By baseline pathogen [8, 59][h]										
MRSA	204/201	81.4	80.6		93.1*	87.1	6.1 (0.5–11.6)	83.3	84.1	
MSSA	268/272	82.8	85.7		86.2	85.3		82.1	84.2	
Streptococcus pyogenes	31/32	67.7	71.9		77.4	75.0		80.6	71.9	
Streptococcus agalactiae	8/12	87.5	100.0		100.0	100.0		87.5	91.7	
Streptococcus dysgalactiae	9/6	77.8	100.0		66.7	83.3		77.8	50.0	
Streptococcus anginosus group	33/45	84.8	88.9		87.9	93.3		75.8	84.4	
Enterococcus faecalis	13/12	84.6	83.3		76.9	66.7		61.5	75.0	

Missing data were considered as treatment failures; endpoints were assessed using a statistical testing hierarchy in the order of composite outcome, post-therapy clinical cure rate and ≥20 % lesion size reduction

IV intravenous, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-susceptible *S. aureus*, *ORI* oritavancin, *pts* patients, *VAN* vancomycin

*$p = 0.032$ vs.VAN

[a] A single IV infusion of ORI 1200 mg over 3 h, followed by IV placebo every 12 h, or IV infusion of VAN 1 g or 15 mg/kg every 12 h for 7–10 days; concomitant aztreonam or metronidazole could be used for suspected Gram-negative and anaerobic pathogens, respectively

[b] Assessed at 48–72 h after initiating therapy

[c] Complete or nearly complete resolution of baseline signs and symptoms such that no further antibacterial treatment was required, assessed by the study investigator 7–14 days after the end of therapy

[d] Cessation of spread or reduction in the size of baseline lesion, absence of fever and no rescue antibacterials required

[e] Modified intent-to-treat population

[f] Primary endpoint

[g] ORI was noninferior to VAN as the lower limit of the 95 % CI was greater than −10 %

[h] Abstract presentation

a clearance of 0.445 L/h; despite the long terminal half-life, AUC_{72h} was 55 % of the overall exposure (i.e. AUC_{∞}) [51].

In healthy volunteers receiving a single dose of 1200 mg, oritavancin nonspecifically and weakly inhibited cytochrome P450 (CYP) enzymes CYP2C9 and CYP2C19,

and weakly induced CYP3A4 and CYP2D6 [8]. Therefore, oritavancin may alter exposure to drugs with a narrow therapeutic window that are mainly metabolized by these enzymes; for example, the mean AUC for warfarin (a CYP2C9 substrate) increased by 31 % with concomitant oritavancin. In vitro, oritavancin is not a substrate or an inhibitor of P-glycoprotein [8].

The pharmacokinetics of oritavancin were not affected to a clinically relevant extent by mild to moderate renal impairment (creatinine clearance >29 mL/min), moderate hepatic impairment (Child-Pugh class B), presence of diabetes, age, height, weight, gender or race; hence, dosage adjustment is not required [8, 51]. The effects of severe renal or hepatic impairment on the pharmacokinetics of oritavancin have not been evaluated [8]. In vitro, oritavancin was not removed from blood by haemodialysis [8], suggesting that dosage adjustment may not be required in patients undergoing haemodialysis.

4 Therapeutic Efficacy of Oritavancin

As stated by Corey et al. [6], two initial phase 3 trials evaluating a daily regimen of intravenous oritavancin (200 or 300 mg daily for 3–7 days) did not provide sufficient evidence for the efficacy and safety of oritavancin in patients with ABSSSI. However in a subsequent randomized, double-blind, multicentre phase 2 study ($n = 302$) in patients with ABSSSI, oritavancin administered as a single 1200 mg dose or 800 mg on day 1 with an optional 400 mg on day 5 was noninferior to a daily regimen (200 mg daily for 3–7 days) in terms of clinical response rates at the test-of-cure visit in the clinically evaluable population (81.5 and 77.5 vs. 72.4 %, respectively) [53]. Based on these results, the efficacy of a single dose of oritavancin 1200 mg was compared with that of twice-daily intravenous vancomycin in two identically designed double-blind, noninferiority, multinational, phase 3 trials (SOLO I [6] and SOLO II [54]) in adults with ABSSSI. Combined analyses of these trials are available as abstracts [55–62] and in the US prescribing information [33]. Discussion in this section focuses on the SOLO trials.

Eligible patients in the SOLO trials were aged ≥18 years and had a diagnosis of ABSSSI (proven or suspected to be caused by a Gram-positive pathogen) that was expected to require ≥7 days of intravenous therapy [6, 54]. The diagnosis of ABSSSI required the presence of a wound infection, cellulitis/erysipelas or major cutaneous abscess, each lesion surrounded by erythema, oedema and/or induration of ≥75 cm^2. At least two signs of ABSSSI (purulent drainage or discharge, erythema, fluctuance, heat or localized warmth, oedema/induration, pain or tenderness to palpation) and one or more signs of systemic inflammation (proximal lymph node swelling and tenderness, body temperature ≥38.0 or <36.0 °C, white blood cell count >10,000 cells/mm^3, bandemia >10 %, or C-reactive protein level above the upper limit of normal) had to be present. Patients without signs of systemic inflammation could be enrolled if they were aged >70 years, had diabetes requiring treatment, or had received immunosuppressive or chemotherapeutic agents in the previous 3 months. Patients who received antibacterials that had activity against Gram-positive pathogens within 14 days prior to randomization were among those excluded [6, 54].

Randomized treatment regimens are shown in Table 2. The primary endpoint was a composite outcome assessed at the US FDA recommended timepoint of 48–72 h in the modified intent-to-treat (mITT) population (Table 2) [6, 54]. Secondary endpoints included early reduction in lesion size and post-therapy clinical cure rate (Table 2), which are recommended by the FDA and the European Medicines Agency, respectively, in ABSSSI trials.

Patient demographic and baseline clinical characteristics did not differ markedly between the treatment groups within each trial [6, 54]. In SOLO I, 49.9 % of patients had cellulitis/erysipelas, 29.5 % had major cutaneous abscess and 20.6 % had wound infection [6]. The corresponding proportions in SOLO II were 30.9, 32.5 and 36.5 %, respectively [54]. At baseline, 19.7 and 9.1 % of patients had diabetes in SOLO I [6] and II [54], respectively. The median lesion size in the oritavancin and vancomycin groups was 248.0 and 225.6 cm^2 in SOLO I [6], and 287.8 and 308.8 cm^2 in SOLO II [6]. A baseline pathogen was isolated in 61.1 and 60.5 % of patients in the oritavancin and vancomycin groups, respectively, in SOLO I, and 69.8 and 70.1 % in SOLO II, with *S. aureus* being the most common [6, 54].

4.1 Individual Trials

Oritavancin was noninferior to vancomycin in terms of the composite outcome at the early clinical evaluation in the mITT population in both SOLO I and II trials (Table 2; primary endpoint) [6, 54]. Similar results were seen in the clinically evaluable population ($n = 791$ [6] and 835 [54] in SOLO I and II). In subgroup analyses of the mITT population, the proportion of patients with major cutaneous abscess achieving the primary endpoint was lower in the oritavancin than in the vancomycin group in SOLO II (81.0 vs. 89.9 %; difference −9.0; 95 % CI −16.5 to −1.4) [54]. Apart from this, in individual trials, there were no significant between-group differences by lesion type, geographic region (North America, Eastern or Western Europe, Asia), risk factors [diabetes or systemic inflammatory response syndrome (SIRS)], age (<65 or ≥65 years), sex, body mass index, race or baseline pathogen (≥1 pathogen, MRSA, MSSA, *S. anginosus* group) [6, 54]. The overall incidence

of treatment failure for the primary endpoint in the oritavancin and vancomycin groups was 14.3 and 16.3 %, respectively, in SOLO I [6] and 17.3 and 14.1 % in SOLO II [54]. The pattern of reasons for the failure was generally similar between the groups, with fever between 48 and 72 h being the most common reason in both groups [6, 54].

Oritavancin was also noninferior to vancomycin with respect to the percentage of patients achieving a ≥20 % reduction in lesion size at 48–72 h and clinical cure rate 7–14 days after the end of therapy in individual trials (Table 2) [6, 54]. In SOLO I, there were no significant between-group differences in lesion size reduction by lesion type and risk factors such as diabetes, SIRS, age ≥65 years or renal insufficiency (abstract presentation [63]), or by baseline MRSA or MSSA [6]. In SOLO II, there were no significant between-group differences in clinical cure rate by lesion type, geographic region, presence of SIRS, age, sex, race, and baseline MRSA or MSSA; however, in patients with diabetes, the clinical cure rate was significantly lower with oritavancin than with vancomycin (69.6 vs. 88.9 %; treatment difference −19.3; 95 % CI −35.5 to −3.2; $n = 46$ and 45) [54].

4.2 Combined Analyses

Combined analyses of SOLO trials also confirmed the efficacy of oritavancin in the overall population and in prespecified subgroups by treatment setting, infection type and baseline pathogen (Table 2). Of note, among patients with baseline MRSA, significantly more oritavancin than vancomycin recipients achieved a ≥20 % reduction in their lesion size at 48–72 h [59].

Oritavancin was effective in the inpatient as well as the outpatient setting, irrespective of ABSSSI severity [56, 62]. In SOLO trials, ≈40 % of patients (all from the USA [62]) were treated entirely in the outpatient setting, and the early and post-therapy clinical outcomes in this population were generally similar to those of the overall population (Table 2) [56]. Clinical outcomes did not differ markedly between treatment groups based on disease severity (Eron class I, II or III) or treatment setting (inpatient or outpatient); the majority (≈71 %) of outpatients were deemed to belong to Eron class II or III, reflecting a moderate level of disease severity [62].

Among inpatients, post-therapy clinical cure rates did not differ markedly between oritavancin and vancomycin recipients in the USA (81 and 78 %; $n = 1165$) and Eastern European countries (86 and 84 %; $n = 202$) [55]. The average length of hospital stay was shorter in the USA (6.0 and 6.4 days, respectively) than in the Eastern European countries (14.9 and 14.7 days) [55].

There was high concordance between early and post-therapy clinical outcomes in SOLO trials, with 87 % of patients who achieved the composite outcome and 85 % of those who achieved a ≥20 % reduction in the baseline lesion size achieving clinical cure at the post-therapy evaluation [60].

Oritavancin produced high microbiological response at the post-therapy evaluation [58]. In the microbiological intent-to-treat population, eradication or presumed eradication rates in the oritavancin and vancomycin groups by baseline pathogen were: MRSA 91.4 and 93.9 %, respectively ($n = 186$ and 181); MSSA 93.2 and 93.9 % ($n = 235$ and 244); *S. pyogenes* 92.6 and 85.2 % ($n = 27$ and 27); *S. anginosus* group 88.5 and 90.5 % ($n = 26$ and 42); and, *E. faecalis* 66.7 and 88.9 % ($n = 12$ and 9) [58].

5 Tolerability of Oritavancin

Oritavancin was generally well tolerated in patients with ABSSSI in SOLO I and II trials, with most treatment-emergent adverse events being mild in severity [6, 8, 54]. Of note, an extended (60 days) safety follow-up for oritavancin did not identify any prolonged or delayed adverse events, suggesting that the extended half-life of oritavancin does not markedly affect its safety profile [6, 54]. In SOLO trials, relatively few patients in the oritavancin and vancomycin groups discontinued treatment because of an adverse event (3.8 vs. 5.8 % [6]; 3.6 vs. 2.6 % [54]). In a pooled analysis of these trials, cellulitis (0.4 %) and osteomyelitis (0.3 %) were the most common adverse reactions leading to discontinuation of oritavancin [8].

In the pooled analysis, 55.3 and 56.9 % of patients in the oritavancin ($n = 976$) and vancomycin ($n = 983$) groups experienced one or more adverse reactions [8]. The most common adverse reactions (incidence ≥1.5 % in the oritavancin group) that occurred in the oritavancin and vancomycin groups were nausea (9.9 vs. 10.5 %), headache (7.1 vs. 6.7 %), vomiting (4.6 vs. 4.7 %), limb or subcutaneous abscess (3.8 vs. 2.3 %), diarrhoea (3.7 vs. 3.4 %), elevated alanine transaminase (2.8 vs. 1.5 %) or aspartate aminotransferase (1.8 vs. 1.5 %), dizziness (2.7 vs. 2.6 %), infusion-site phlebitis (2.5 vs. 1.5 %), tachycardia (2.5 vs. 1.1 %) and infusion-site reaction (1.9 vs. 3.5 %) [8]. Where reported [6], Red-Man syndrome did not occur in oritavancin recipients. In SOLO I and II, osteomyelitis was reported as an adverse event in six oritavancin recipients and one vancomycin recipient in total [6, 54]. Treatment-related adverse events occurred in less than one-third of patients in the oritavancin and vancomycin groups (22.8 vs. 31.4 % [6]; 21.7 vs. 25.5 % [54]).

Serious adverse reactions occurred in ≈6 % of patients in both treatment groups, with cellulitis being the most common (≈1 % in both groups) [8]. There were no reports of serious elevations in liver enzymes or discontinuation of

study drugs because of these adverse events [6, 54]. Two patients in the oritavancin group and three patients in the vancomycin group died during SOLO trials; no deaths were considered to be related to study drug by the investigator [6, 54].

In a pooled analysis of SOLO trials, the distribution of time to onset and duration of adverse events were generally similar between oritavancin and vancomycin groups [64]. The median time to onset and the duration was 2.0 and 2.0 days for oritavancin-related adverse events, and 1.0 and 6.0 days for oritavancin-related serious adverse events [64].

The incidence of laboratory abnormalities, vital signs and electrocardiographic findings did not differ markedly between oritavancin and vancomycin recipients [6, 54]. In a thorough QT study in healthy volunteers ($n = 135$), a single 1600 mg dose of oritavancin did not prolong the corrected QT interval to a clinically relevant extent [8].

In the two initial phase 3 trials (Sect. 4), once-daily oritavancin was not associated with potential glycopeptide-related adverse events, such as nephrotoxicity, ototoxicity, vestibular toxicity or haematologic toxicity [65].

6 Dosage and Administration of Oritavancin

Intravenous oritavancin is approved in the USA [8] and EU [9] for the treatment of ABSSSI in adults. In the USA, it is indicated for patients with ABSSSI caused or suspected to be caused by susceptible isolates of specific Gram-positive bacteria (Table 1). In order to reduce the risk of antibacterial resistance and maintain the effectiveness of oritavancin and other antibacterial drugs, oritavancin should only be used to treat infections that are proven or strongly suspected to be caused by susceptible bacteria [8, 9].

The recommended dosage of oritavancin is a single 1200 mg administered as a 3-h infusion [8, 9]. Infusion related reactions, such as pruritus, urticaria or flushing, can occur with oritavancin; if they occur, slowing or interrupting the infusion should be considered. Oritavancin should be used in patients taking chronic warfarin only when the benefits outweigh the risks of bleeding. The drug may artificially prolong activated partial thromboplastin time for up to 48 h, and prothrombin time and International Normalized Ratio for up to 24 h. *Clostridium difficile*-associated diarrhoea (CDAD) can occur with systemic antibacterial drugs, including oritavancin, and therefore, patients should be evaluated for CDAD if diarrhoea occurs during treatment. Patients should be monitored for signs and symptoms of osteomyelitis, and if osteomyelitis is diagnosed or suspected, an appropriate alternate antibacterial therapy should be initiated. Use of intravenous unfractionated heparin sodium is contraindicated for 48 h after oritavancin administration and oritavancin is contraindicated in patients with a hypersensitivity to oritavancin [8, 9]. Local prescribing information should be consulted for detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

7 Place of Oritavancin in Acute Bacterial Skin and Skin Structure Infections

Current Infectious Diseases Society of America practice guidelines for the management of severe skin and soft tissue infections recommend a number of parenteral empirical treatment options, including vancomycin, daptomycin, linezolid, telavancin, ceftaroline and clindamycin [4]. As oritavancin was approved only recently, it was not included in these guidelines, nor were dalbavancin and tedizolid. There are no specific treatment guidelines for ABSSSI in Europe. However, a retrospective assessment of clinical practice patterns in Europe during 2010–2011 found that the majority of hospitalized adult patients with ABSSSI who required intravenous therapy were initially treated empirically ($\approx$82 %; $n = 1995$), most commonly with penicillins with or without a β-lactamase inhibitor ($\approx$60 %) [2]. Vancomycin, daptomycin and linezolid were the most commonly used anti-MRSA agents. Of note, $\approx$40 % of patients required their initial therapy to be subsequently modified and the most common reason for this was insufficient clinical response or treatment failure (17 %) [2].

Oritavancin has multiple mechanisms of action resulting in rapid, concentration-dependent bactericidal activity in vitro (Sect. 2.1). It shows potent in vitro activity against susceptible Gram-positive pathogens associated with ABSSSI (Table 1) and has a low potential for the emergence of bacterial resistance (Sect. 2.3). Oritavancin is also active against VISA, VRSA and VRE; unlike other glycopeptides, it retains its activity against VanA-type VRE (Sect. 2.2.1).

The prolonged plasma terminal half-life (245 h) of oritavancin allows for convenient single-dose therapy for ABSSSI (Sect. 3). Dalbavancin also has a prolonged terminal half-life (mean 348–372 h), although it was evaluated only as a two-dose regimen in key clinical trials [66]. In comparison, telavancin is administered once daily [67] and vancomycin every 6 or 12 h [68] for up to 14 days.

Oritavancin dosage adjustment is not required for moderate renal or hepatic impairment, age, weight, gender or race, while the other glycopeptides require dosage adjustment for renal impairment [66–68]. Although, penetration of oritavancin into skin blister fluid is modest

relative to dalbavancin [66] or telavancin [67], oritavancin concentration in blister fluid exceeds its MIC_{90} value of *S. aureus*. There is a potential risk of bleeding with concomitant use of oritavancin and warfarin. The safety of oritavancin in ABSSSI patients receiving chronic warfarin treatment is currently being evaluated in a phase 4 clinical trial (NCT02452918). Oritavancin is also known to interfere with some coagulation tests. While potential drug–drug or drug-laboratory test interactions are also reported for vancomycin [68] and telavancin [67], dalbavancin has a low potential for such interactions [69].

In two large phase 3 registration (SOLO I and II) trials in adult patients with ABSSSI, oritavancin was noninferior to vancomycin in terms of the primary composite outcome at an FDA-recommended early timepoint of 48–72 h after initiating therapy, with ≥79 % of patients in both treatment groups achieving this endpoint (Sect. 4). Similar results were reported for various subgroup analyses in either one or both trials. Oritavancin was also noninferior to vancomycin in terms of a ≥20 % reduction from baseline in lesion size at the early timepoint and clinical cure rate 7–14 days after the end of therapy. There was good concordance between early and post-therapy clinical outcomes. Oritavancin was also effective in the outpatient setting, including in patients with severe ABSSSI. In the absence of head-to-head comparative studies, a Bayesian network meta-analysis of 52 randomized controlled trials suggests that most antibacterials used for the treatment of ABSSSI, including oritavancin, may have similar efficacy [70].

Oritavancin was generally well tolerated in adults with ABSSSI in SOLO trials, with most treatment-emergent adverse events being of mild severity (Sect. 5). The most common adverse reactions occurring in oritavancin recipients included nausea, headache, vomiting, limb and subcutaneous abscesses, and diarrhoea. Treatment-related adverse events occurred in less than one-quarter of oritavancin recipients, with <4 % of patients discontinuing treatment because of an adverse reaction. Overall, the safety profile of oritavancin was similar to that of vancomycin. The extended plasma half-life of oritavancin was not associated with any prolonged or delayed adverse events in SOLO trials. However, the safety of oritavancin in real-world clinical use remains to be seen.

CDAD, hypersensitivity and infusion related reactions have been known to occur with most glycopeptide antibacterials, including oritavancin (Sect. 5). In SOLO trials, more cases of osteomyelitis were reported with oritavancin than with vancomycin (6 vs. 1); however, in SOLO II, all five cases in the oritavancin group occurred within 1–9 days after treatment, suggesting that osteomyelitis may have been present at time of screening [54]. Specific adverse events with other glycopeptide antibacterials include nephrotoxicity with vancomycin and telavancin [67], and elevated alanine transaminase levels with dalbavancin [69]. Telavancin also has a boxed warning for foetal risk, based on animal studies [67].

Budget impact model analyses (abstract presentations) conducted from a USA [71] and UK [72] hospital perspective suggest that using oritavancin in some patients (≈26 and ≈4 %, respectively) with moderate to severe ABSSSI or skin and soft tissue infections would reduce the total annual cost of medical care relative to the current clinical practice, driven by reduced healthcare resource utilization. However, the cost effectiveness of oritavancin relative to the standard-of-care agents in ABSSSI is yet to be established.

In conclusion, intravenous oritavancin was effective and generally well tolerated in adult patients with ABSSSI in two, large well-controlled clinical trials. The convenient single-dose therapy with oritavancin may provide some advantages: shorter, or elimination of, hospital stays, which may also reduce the risk of nosocomial infections; a reduction in healthcare resource utilization and cost; potential for use in outpatient parenteral antimicrobial therapy; no need for peripherally inserted central catheters; and, elimination of patient compliance concerns, complex therapeutic drug monitoring and dosage adjustments. However, head-to-head clinical studies and robust pharmacoeconomic analyses are required to definitively position this drug relative to other antibacterials used for ABSSSI.

Data selection sources: Relevant medical literature (including published and unpublished data) on oritavancin was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 7 September 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Oritavancin, Nuvocid, ORBACTIV, LY 333328, skin.
Study selection: Studies in patients with acute bacterial skin and skin structure infections who received oritavancin. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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Compliance with Ethical Standards

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