New Medicine Assessment

ORITAVANCIN

Recommendation: RED for the following indications:

Treatment of acute, complicated bacterial skin and skin structure infections (ABSSSI) in adults, with confirmed drug-resistant gram-positive infection, who are eligible for early discharge.

Use must be on the advice of local microbiologists and must be reserved for the treatment of patients who would otherwise be required to have a prolonged inpatient stay due to unsuitability for OPAT.

Summary of supporting evidence:

- NICE consider oritavancin as an 'option' for ABBBSI when standard oral and intravenous antibiotics are not suitable.
- SMC has approved oritavancin for restricted use within NHS Scotland for patients with confirmed or suspected MRSA infection who are eligible for early discharge.
- Both randomised, phase III, double-blind studies (SOLO I/SOLO II) demonstrated non-inferiority for oritavancin vs. vancomycin.
- Comparative data to antimicrobials other than vancomycin is lacking. In particular, data comparing oritavancin to teicoplanin.
- Oritavancin does not have any antibacterial properties that could be viewed as definite and proven advantages over other intravenous agents that have antibacterial spectra confined to certain Gram-positive organisms.
- Oritavancin has demonstrated good activity against vancomycin-resistant enterococci (VRE) in vitro.
- Oritavancin offers a treatment option for MRSA positive soft tissue infections.
- The SOLO I and SOLO II trials were not powered to detect non-inferiority in the MRSA subgroup.
- The SOLO I/SOLO II study populations lacked diversity in patient characteristics and co-morbidities. They also did not have UK participation, therefore may not be representative of UK MRSA prevalence or follow standard UK antimicrobial protocols.
- Oritavancin resistance data in the UK is limited.
- Oritavancin is administered as one dose and as such offers the potential for no inpatient stay and no requirement for the OPAT service.
- Oritavancin does not require a peripherally inserted central catheter, and patients will not need to maintain vascular access for daily administrations of antibiotic therapy.
- The extended half life may remove the need to use an oral antibiotic to complete a course of therapy.
- Oritavancin does not require monitoring (e.g. of blood levels, renal function, full blood counts) or dose adjustment, and has no significant drug interactions. Although it should be noted that it can affect the results of some laboratory coagulation tests.
- ADRs appear to be mainly self-limiting, but there are concerns over increased prevalence of osteomyelitis and of abscesses during oritavancin treatment. These have been noted on the SPC.
- Due to the long terminal half life (245 hours) there is a potential for delayed hypersensitivity reactions after the patient has been discharged from care and a potential for the effect to persist for weeks.
- Intravenous infusions of oritavancin can cause reactions that resemble "red man syndrome".
- There is limited experience in clinical studies in patients with bacteraemia, peripheral vascular disease or neutropenia, in immunocompromised patients, in patients aged > 65 years and in infections due to S. pyogenes.

Details of Review

Name of medicine (generic & brand name)**:**[1] Oritavancin (Tenkasi) 400 mg powder for concentrate for solution for infusion
Strength(s) and form(s):1 Powder for concentrate for solution for infusion (powder for concentrate). Each vial contains oritavancin diphosphate equivalent to 400 mg oritavancin. After reconstitution, 1 ml of the solution contains 10 mg oritavancin. After dilution, 1 ml of the solution for infusion contains 1.2 mg oritavancin.
Dose and administration:1 1,200 mg administered as a single dose by intravenous infusion over 3 hours.
BNF therapeutic class / mode of action:[2] Oritavancin is a glycopeptide antibacterial; it has bactericidal activity against Gram-positive bacteria including various staphylococci. However, there are reports of Staphylococcus aureus with reduced susceptibility to glycopeptides and increasing reports of glycopeptide-resistant enterococci.
Licensed indication(s): Treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.
Proposed use (if different from, or in addition to, licensed indication above): Treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.
Course and cost: NHS indicative price = £1500 for 1 dose (3 x 400mg vials) As per BNF Oct 2022

Current standard of care/comparator therapies:

NICE and Public Health England prescribing guidance recommends the following to treat cellulitis and erysipelas in adults:[3]

Antibiotic[1]	Dosage and course length	
First choice antibiotic (give oral unless person unable to take oral or severely unwell)[2]		
Flucloxacillin	500 mg to 1 g four times a day orally[3] for 5 to 7 days[4]	**or** 1 to 2 g four times a day IV[5]
Alternative first choice antibiotics for penicillin allergy or if flucloxacillin unsuitable (give oral unless person unable to take oral or severely unwell)[2]		
Clarithromycin	500 mg twice a day orally for 5 to 7 days[4]	**or** 500 mg twice a day IV[5]
Erythromycin (in pregnancy)[6]	500 mg four times a day orally for 5 to 7 days[4]	
Doxycycline	200 mg on first day, then 100 mg once a day orally for 5 to 7 days in total[4]	
First choice antibiotic if infection near the eyes or nose[7] (consider seeking specialist advice; give oral unless person unable to take oral or severely unwell)[2]		
Co-amoxiclav	500/125 mg three times a day orally for 7 days[4]	**or** 1.2 g three times a day IV[5]
Alternative first choice antibiotics if infection near eyes or nose[7] for penicillin allergy or if co-amoxiclav unsuitable (consider seeking specialist advice; give oral unless person unable to take or severely unwell)[2]		
Clarithromycin ***with***	500 mg twice a day orally for 7 days[4]	**or** 500 mg twice a day IV[5]
Metronidazole	400 mg three times a day orally for 7 days[4]	**or** 500 mg three times a day IV[5]
Alternative choice antibiotics for severe infection		
Co-amoxiclav	500/125 mg three times a day orally for 7 days[4]	**or** 1.2.g three times a day IV[5]
Cefuroxime	750 mg to 1.5 g three or four times a day IV[5]	
Clindamycin	150 to 300 mg four times a day (can be increased to 450 mg four times a day) orally for 7 days[4]	**or** 600 mg to 2.7 g daily IV in two to four divided doses, increased if necessary in life-threatening infection to 4.8 g daily (maximum per dose 1.2 g)[5]
Ceftriaxone (only for ambulatory care[8]	2 g once a day IV[5]	
Antibiotics to be added if MRSA infection suspected or confirmed (combination therapy with an antibiotic listed above)[8]		
Vancomycin[9,10]	15 to 20 mg/kg two or three times a day IV (maximum 2 g per dose), adjusted according to serum vancomycin concentration[5]	
Teicoplanin[9,10]	Initially 6 mg/kg every 12 hours for three doses, then 6 mg/kg once a day IV[5]	
Linezolid (if vancomycin or teicoplanin cannot be used; specialist use only)[10]	600 mg twice a day orally	**or** 600 mg twice a day IV[5]

[1] See BNF for use and dosing in specific populations, for example, hepatic and renal impairment, pregnancy and breast-feeding, and administering intravenous (or intramuscular) antibiotics.
[2] Give oral antibiotics first-line if the person can take oral medicines, and the severity of their symptoms does not require intravenous antibiotics.
[3] The upper dose of 1 g four times a day would be off-label. Prescribers should follow relevant professional guidance, taking full responsibility for the decision, and obtaining and documenting informed consent. See the GMC's Good practice in prescribing and managing medicines for more information.
[4] A longer course (up to 14 days in total) may be needed based on clinical assessment. However, skin does take time to return to normal, and full resolution at 5 to 7 days is not expected.
[5] If intravenous antibiotics are given, review by 48 hours and consider switching to oral antibiotics if possible for the appropriate course length.
[6] Erythromycin is preferred if a macrolide is needed in pregnancy, for example, if there is true penicillin allergy and the benefits of antibiotic treatment outweigh the harms. See the Medicines and Healthcare products Regulatory Agency (MHRA) Public Assessment Report on the safety of macrolide antibiotics in pregnancy
[7] Infection around the eyes or the nose (the triangle from the bridge of the nose to the corners of the mouth, or immediately around the eyes including periorbital cellulitis) is of more concern because of risk of a serious intracranial complication.
[8] Other antibiotics may be appropriate based on microbiological results and specialist advice.
[9] See BNF for information on therapeutic drug monitoring.
[10] See BNF for information on monitoring of patient parameters.

https://www.nice.org.uk/guidance/ng141/resources/visual-summary-pdf-6908401837

Relevant NICE guidance:

- **NICE and PHE Summary of antimicrobial prescribing guidance – managing common infections** (2022)[4]
- **NG141 Cellulitis and erysipelas** (2019)[3]
  See notes above – 'Current standard of care/comparator therapies'.
- **ES39 Antimicrobial prescribing: oritavancin for acute bacterial skin and skin structure infections** (2022)[5]
  See notes below – 'Summary of evidence'

Background and context

A skin and skin structure infection is a bacterial infection of skin and associated tissues. Acute bacterial skin and skin structure infections (ABSSSI) are common and encompass a variety of disease presentations and severity. Increased antimicrobial resistance among both Gram-positive and Gram-negative bacteria with methicillin-resistant *Staphylococcus aureus* is the main problem in treatment.[6]

ABSSSI may require systemic antibiotics, surgical management, and hospitalisation.[5] Some systemic courses of antimicrobials may be administered outside of the hospital setting, for example in the patient's home.

Following the emergence of strains with reduced susceptibility to vancomycin (first generation of glycopeptide), the second generation of semisynthetic lipoglycopeptides has been developed as alternatives for treating MRSA infections. Examples include dalbavancin and oritavancin. Lipoglycopeptides are semisynthetic derivatives characterized by adding a lipophilic side chain, which prolongs their half-lives and increases their activities against Gram-positive cocci.[7]

Oritavancin is a single-dose antibiotic which has a marketing authorisation for treating acute bacterial skin and skin structure infections (ABSSSI) in adults. It has activity against Gram-positive bacteria, causing rapid bacterial cell death through inhibition of cell wall biosynthesis and disruption of membrane integrity. Oritavancin was launched in the US in October 2014.[8]

Summary of evidence

Summary of efficacy data in proposed use:

ES39 Antimicrobial prescribing: oritavancin for acute bacterial skin and skin structure infections (2022)[5]

Advisory statement on likely place in therapy

Oritavancin may be an option for adults needing treatment in hospital, ambulatory care or through outpatient parental antimicrobial therapy (OPAT) for severe ABSSSI (cellulitis or erysipelas, abscesses and wound infections) when standard oral and intravenous antibiotics are not suitable. Take account of local antimicrobial resistance and seek specialist microbiological advice.

Oritavancin offers the potential for treating skin infections caused by gram-positive pathogens, including MRSA. There is no known cross-resistance between oritavancin and non-glycopeptide classes of antibiotics. Also, oritavancin does not require any dose adjustment for age, weight, or mild to moderate renal function. Therapeutic drug monitoring is not required and it is administered as a single dose treatment course.

Limitations of the evidence from the submitted studies

The majority of people included in the studies were male, aged less than 65 years and of white ethnicity. People who were immunocompromised or had suspected sepsis or had elevated liver function tests (≥3 times the upper limit of normal [ULN] or total bilirubin ≥2 times the ULN) were excluded from enrolment. Therefore, the study results may not be representative of some populations.

All people in the studies had cellulitis or erysipelas, abscesses or wound infections as per the inclusion criteria. Further studies would be required to assess effectiveness in other infections such as bacteraemia, osteomyelitis and joint infections.

The studies did not report how many people had received antibiotics for their infection prior to enrolling in the study.

The UK was not a participating country, therefore the proportion of patients with MRSA in the studies may not be reflective to the UK.

Aztreonam and metronidazole, which could be used for mixed infection in the studies, are not standard treatment options for severe infections in the NICE guideline.

Public Health England's guidance start smart then focus and the NICE guideline on antimicrobial stewardship recommend that intravenous antibiotic prescriptions should be reviewed at 48 to 72 hours, documenting response to treatment and any available microbiology results to determine whether the

antibiotic should be continued or switched to a narrower spectrum or an oral antibiotic. In both studies, people in the vancomycin arm were not reviewed at 48 to 72 hours for consideration of oral antibiotics.

Oritavancin is a new antimicrobial and therefore data on resistance and impact on clinical practice in the UK are limited.

Scottish Medicines Consortium (2022)[9]

Oritavancin (Tenkasi®) is accepted for restricted use within NHSScotland (following resubmission).

SMC restriction: patients with confirmed or suspected methicillin-resistant Staphylococcus aureus (MRSA) infection who are eligible for early discharge. Use should be on the advice of local microbiologists or specialists in infectious disease.

In two randomised, phase III, double-blind studies of patients with ABSSSI, oritavancin was non-inferior to a glycopeptide antibiotic for clinical cure at the end of treatment in the clinically evaluable population.

There are no comparative data available with other treatments currently used in Scottish clinical practice (for example IV teicoplanin, IV daptomycin, IV dalbavancin or oral linezolid). Therefore, the submitting company presented a Bayesian network meta-analyses (NMAs) that included 39 studies and compared treatments for a range of clinical and safety outcomes. The NMAs allowed a comparison of oritavancin versus various comparators including IV daptomycin, IV dalbavancin and oral linezolid. In addition, clinical response, early response and microbiological response were also assessed in the subgroup of patients with MRSA. The submitting company concluded that the NMAs demonstrated non-inferiority of oritavancin, compared with available treatments, for the majority of efficacy and safety outcomes and that there were no results demonstrating a significant difference between oritavancin and any other alternative treatment in composite clinical response in the full or MRSA populations. It was not possible to include teicoplanin in the network since no studies including teicoplanin for the treatment of complicated infections were found in the systematic literature review.

Only 21% (204/978) of patients in the oritavancin groups of SOLO I and II were positive for MRSA, and the studies were not powered to detect non-inferiority in this subgroup. Patients were excluded from the studies if they received prior treatment with systemic or topical antibacterials with activity against Gram-positive pathogens within the previous 14 days so the treatment pathway does not correlate with the proposed positioning in patients previously treated with flucloxacillin and vancomycin.

The cost-minimisation analysis reported that the cost per patient for treating ABSSSI from empiric treatment through to clinical cure with oritavancin was £5,066. The cost of dalbavancin was £5,352 whereas the cost of teicoplanin, daptomycin and linezolid were £4,652, £4,973 and £4,068 respectively. On the basis of these findings, oritavancin was cost minimising compared to dalbavancin but not against the other comparators (which are administered as multiple doses).

	Oritavancin	Dalbavancin	Teicoplanin	Daptomycin	Linezolid
Medication costs (£)	1,798	1,974	349	670	832
Inpatient costs (£)	3,236	3,236	3,236	3,236	3,236
OPAT costs (£)	-	133	1,067	1,067	-
Outpatient costs (£)	32	8	-	-	-
Total (£)	5,066	5,352	4,652	4,973	4,068
Treatment days	7	8	12	12	12
Inpatient days	6	6	6	6	6
Cost per treatment day avoided	-	Oritavancin is dominant	83	19	200
Incremental cost per patient comparator versus oritavancin	-	£286	-£414	-£93	-£998

OPAT= outpatient parenteral antibiotic therapy

The main weakness in the economic analysis results from the lack of direct comparative data for oritavancin against the relevant comparators in the proposed positioning, such as daptomycin, teicoplanin, dalbavancin and linezolid. This gives rise to uncertainty around the estimate of clinical cure rates at PTE which has been applied across all comparators. This limitation is further heightened since the trials (SOLO I & SOLO II) from which clinical cure rates have been estimated were not powered to test the non-inferiority of oritavancin by pathogen subgroups, including the MRSA subgroup. Sensitivity analysis highlighted the sensitivity around this parameter as it has the maximum influence on base case incremental costs.

European Medicines Agency (2015)[10]

There are 2 main clinical studies in the submission: SOLO I[11] and SOLO II[12]. These are multicentre, double-blind, randomised studies to evaluate the efficacy and safety of single-dose IV oritavancin versus IV vancomycin for the treatment of patients with acute bacterial skin and skin structure infection. Both studies were of identical design and were initiated in 2011.

Eligible adult patients were to have a diagnosis of ABSSSI suspected or confirmed to be caused by a Gram-positive pathogen and expected to require at least 7 days of IV therapy. A specimen for culture was obtained within 24 h of the first dose of study drug.

ABSSSI included one of the following infections: wound infections, cellutlitis/erysipelas, major cutaneous abscess. Oritavancin was given on Day 1 as a single 1200 mg dose. Vancomycin was administered IV for 7 to 10 days. The first dose on Day 1 was administered as 1 g or 15 mg/kg over 3 h and then as 1 g or 15 mg/kg q12h. Subsequent doses could be adjusted by the unblinded pharmacist based on CrCl levels, clinical status or vancomycin trough levels. Aztreonam and metronidazole were allowed for patients with mixed infections.

The primary objective as stated in the protocol was to establish non-inferiority of oritavancin vs. vancomycin based on the primary efficacy outcome of cessation of spread or reduction in size of the baseline lesion, absence of fever and no rescue medication at Early Clinical Evaluation. The critical secondary objective was to evaluate the clinical response vs. vancomycin at End of Therapy (EOT) and sustained to Day 10 and the post therapy evaluation (PTE).

In SOLO I there were 954 treated patients, predominantly white and male. Most patients (98.7%) in the oritavancin group received a full dose of 1200 mg on Day 1 and 88.6% completed the twice daily placebo infusions for 7 to 10 days. Slightly fewer (83.9%) in the vancomycin group completed 7 to 10 days of therapy. Less than 10% received aztreonam and/or metronidazole.

A sustained clinical response at PTE was observed for 65.9% oritavancin and 67.2% vancomycin MITT patients (difference -1.3%; 95% CI -7.3, 4.7). Failure was reported for 25.3% and 25.1% while data were missing for 8.8% and 7.7%. If missing values were excluded the rates were 72.3% vs. 72.9% and if they were treated as success the rates were 74.7% vs. 74.9%. The microbiological success rates were comparable between treatment groups by type of infection.

In SOLO II there were 1005 treated patients, predominantly white and male. Most patients (93.8%) in the oritavancin group received a full dose of 1200 mg on Day 1 and 90.3% completed the twice daily placebo infusions for 7 to 10 days. Slightly fewer (88.8%) completed 7 to 10 days of vancomycin. Aztreonam was given to ~8% per group and metronidazole to 6.4% and 4.4%. The percentages who failed and reasons for treatment failure were similar between groups.

A sustained clinical response at PTE was observed for 74.4% oritavancin and 73.7% vancomycin patients (difference -0.6%; 95% CI -4.8, 6.1). Failure was reported for 18.1% and 15.7% while data were missing for 7.6% and 10.6%. If missing values were excluded the rates were 80.4% vs. 82.4% and if they were treated as success the rates were 81.9% vs. 84.3%. The microbiological success rates were comparable between treatment groups by type of infection.

Both studies demonstrated non-inferiority for oritavancin vs. vancomycin. Oritavancin does not have any antibacterial properties that could be viewed as definite and proven advantages over other intravenous agents that have antibacterial spectra confined to certain Gram-positive organisms. However, it offers a single parenteral treatment with efficacy against ABSSSI that was shown to be comparable to that of vancomycin in two adequately powered Phase 3 studies.

Brown et al (2021)[13]

Treatment of methicillin-resistant Staphylococcus aureus (MRSA): updated guidelines from the UK.

Updating the national guidelines relating to MRSA was a joint initiative of BSAC, British Infection Association (BIA), Healthcare Infection Society (HIS) and Infection Prevention Society (IPS).

Other skin and skin structure infections

Consider recently licensed agents such as ceftaroline, delafloxacin, oritavancin, or telavancin as alternative options for treatment of cellulitis/soft tissue infection caused by MRSA (weak recommendation).

Estrada et al (2020)[14]

The purpose of this report was to describe the results of two separate multicentre observational cohort studies that described the outcomes associated with two unique real-world usage patterns of oritavancin.

The first cohort (n=115) examined patients 18 years or older who were treated with oritavancin at three outpatient sites for SSTIs caused by suspected or confirmed Gram-positive pathogens, including MRSA, to avoid hospital admission. Patients were included if they had not been discharged from the inpatient setting within the previous 24 h and received their single-dose oritavancin treatment at a hospital-based outpatient infusion centre. The primary outcomes measured were 30-day healthcare costs and admissions (all cause and infection related). The second cohort (n=151) was a multi-centre, retrospective chart review of adult patients who were discharged early from seven hospitals in 2015 on oritavancin for SSTIs. The primary outcome was readmission of patients within 30 days (all cause and infection related).

In cohort one, of the 56 patients with baseline culture results, MRSA was identified in 27 (48.2%). The infection types were cellulitis (70%), wound (19%), and major cutaneous abscess (11%). Eleven patients (9.6%) received antibiotics within 30 days post index treatment. Reasons for antibiotic use included inadequate treatment response (n=1), relapse of the same infection (n=2), new Gram-positive infection (n=2), the primary infection was both Gram positive and Gram negative (n=4), and standard of care or hospital protocol (n=3). Seven patients (6.1%) were admitted to hospital within 30 days of the index treatment. Three of these admissions (2.6% overall) were due to an infection, with Gram-negative bacteria identified, and required antibiotic therapy. None of the three patients who were hospitalized with a Gram-negative infection had received antibiotics with Gram-negative activity previously.

In cohort two, among patients with available culture results (n=78), MRSA (32 patients) was the most common pathogen. Most patients received vancomycin (78%) prior to discharge with oritavancin. Other frequently used antibiotics prior to oritavancin were clindamycin (11%), ceftaroline (9%), daptomycin (7%), and linezolid (5%). Seven patients received concomitant antimicrobials with oritavancin for the treatment of Gram-negative organisms. Ten patients (6.6%) were readmitted at 30 days, and 4 of those readmissions (2.6%) were attributable to infection. Of those 4, 2 patients were admitted to treat a Gram-negative infection, and 2 patients were admitted for abscess drainage (1 was found to be MSSA and the other was culture negative). The two patients with Gram-negative infections received inappropriate antibiotic therapy for Gram-negative pathogens prior to the administration of oritavancin.

Summary of product characteristics[1]

Gram-negative organisms are intrinsically resistant to all glycopeptides, including oritavancin.

Resistance to oritavancin was observed *in vitro* in vancomycin-resistant isolates of *Staphylococcus aureus*. There is no known cross-resistance between oritavancin and non-glycopeptide classes of antibiotics.

Oritavancin exhibits reduced *in vitro* activity against certain Gram-positive organisms of the genera *Lactobacillus*, *Leuconostoc* and *Pediococcus* that are intrinsically resistant to glycopeptides.

Efficacy has been demonstrated in clinical studies against the following pathogens that were susceptible to oritavancin *in vitro*.

Gram-positive microorganisms:

• *Staphylococcus aureus*

• *Streptococcus pyogenes*

• *Streptococcus agalactiae*

• *Streptococcus dysgalactiae*

• *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*)

Clinical efficacy has not been established against the following pathogens although *in vitro* studies suggest that they would be susceptible to oritavancin in the absence of acquired mechanisms of resistance:

• Beta-haemolytic streptococci of Group G

• *Clostridium perfringens*

• *Peptostreptococcus* spp.

In humans, less than 1% to 5% of the dose was recovered as parent drug in faeces and urine respectively after 2 weeks of collection indicating that oritavancin is slowly excreted unchanged. The mean terminal elimination plasma half-life of oritavancin is 245 hours.

Saravolatz et al (2015)[15]

Overall, there is very good activity of oritavancin against common gram-positive pathogens. Oritavancin's antimicrobial activity is reduced when vancomycin activity is reduced, with minimum inhibitory concentration of 90% (MIC90) of 1 µg/mL and 2 µg/mL for VRSA and VISA, respectively. Noteworthy is the activity against vancomycin-resistant enterococci (VRE), which has become problematic in many hospital settings in the United States. In addition, oritavancin is active against Micrococcus species, Listeria monocytogenes, and Corynebacterium species, each with MIC90 < 0.06 µg/mL. Oritavancin is also active against anaerobic gram-positive organisms that include Clostridium difficile (MIC90 = 1 µg/mL), Clostridium perfringens (MIC90 = 1 µg/mL), Peptostreptococcus species (MIC90 = 0.5 µg/mL), Peptococcus species (MIC90 = 0.5 µg/mL), Propionibacterium acnes (MIC90 = 0.25 µg/mL).

Oritavancin has demonstrated in vitro synergy against staphylococci when combined with gentamicin, linezolid, moxifloxacin, and rifampin. The addition of gentamicin combined with oritavancin demonstrated in vitro synergistic bactericidal activity against VRE, including both VanA and VanB phenotypes.

Comparative In Vitro Minimum Inhibitory Morbidity Concentrations of Oritavancin for Gram-Positive Organisms

Organism	Oritavancin	Vancomycin	Daptomycin	Telavancin	Dalbavancin
MSSA	0.06	1	0.5	0.06	0.06
MRSA	0.06	1	0.5	0.06	0.06
VISA	2	8	4	0.75	. . .
VRSA	1	>64	1	6	. . .
CoNS	0.06	2	0.5	0.06	0.06–0.12
Vancomycin susceptible					
Enterococcus faecalis	0.03	2	2	0.16	0.06
Enterococcus faecium	<0.008	1	4	0.06	0.12
Vancomycin resistant (VanA)					32–>128
E. faecalis	0.5	>16	1	. . .	. . .
E. faecium	0.12	>16	2	2	. . .
Vancomycin resistant (VanB)					0.12–1
E. faecalis	0.03	>16	2	. . .	. . .
E. faecium	≤0.008	>16	2	8	. . .
Streptococcus pneumoniae	≤0.008	≤1	. . .	≤0.015	≤0.03–0.06
Viridans group streptococci	0.03	1	1	0.03	0.016–0.03
β-hemolytic streptococci	0.12	0.5	0.25	0.06	0.015–0.06

Data are presented as MIC_{90s} (µg/mL).

Abbreviations: CoNS, coagulase-negative staphylococci; MIC_{90}, minimum inhibitory concentration of 90%; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; VISA, vancomycin-intermediate *Staphylococcus aureus*; VRSA, vancomycin-resistant *Staphylococcus aureus*.

Summary of safety data:

European Medicines Agency (2015)[10]

In the SOLO pool the most common AEs in the oritavancin group were nausea, headache and vomiting. The rates for any individual AE in the oritavancin group were ≤ 10% and mostly similar to rates in the

vancomycin group.

The incidence of AEs possibly representing hypersensitivity reactions was lower in the oritavancin group (12.1%) than the vancomycin group (18.6%).

The incidence of vestibular toxicity was similar in the oritavancin (2.0%) and vancomycin (2.8%) groups in and dizziness was the most frequent individual AE.

Overall rates for hepatic AEs (related to liver laboratory abnormalities or clinical AEs) were 4.7% in the oritavancin group and 3.0 % in the vancomycin group. The difference was driven by AEs of increased ALT in 2.8% oritavancin and 1.5% vancomycin patients.

The incidence of renal AEs was similar in the oritavancin (0.7%) and vancomycin (0.9%) groups. Renal failure was reported for 3 in the oritavancin group and 5 in the vancomycin group (one of the 5 was serious).

Cardiac AE rates were 3.4% for oritavancin and 2.7% for vancomycin, with a higher rate of tachycardia with oritavancin (2.5% vs. 1.1%).

Osteomyelitis occurred more often with oritavancin (6 cases) than vancomycin (one case) in the SOLO studies (including 5 vs. 0 in SOLO II), a pattern which was already apparent from the prior studies that employed daily dosing. An individual patient review of all osteomyelitis cases did not reveal any common factor to explain the imbalance in osteomyelitis between the treatment groups.

In addition, in the SOLO studies the rates of abscesses (total of abscess and abscess in limb) were 3.9% for oritavancin vs. 1.9% for vancomycin while the difference in the phase 3 daily dosing studies was 3.3% vs. 2.6%. Most of these were treatment-emergent rather than worsening of a baseline abscess. These imbalances have not been explained.

There were 77 deaths (oritavancin 1.8% [53/3017]; vancomycin/comparator 1.2% [24/1954]) reported across all studies. None of the deaths was considered related to study drug by the investigator.

Summary of Product Characteristics[1] [NB. For complete product information please refer directly to the SPC]

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Use of intravenous unfractionated heparin sodium is contraindicated for 120 hours (5 days) after oritavancin administration because the activated partial thromboplastin time (aPTT) test results may remain falsely elevated for up to 120 hours after oritavancin administration.

Special warnings and precautions for use

- Hypersensitivity reactions - Serious hypersensitivity reactions, including anaphylactic reactions and anaphylactic shock have been reported with the use of oritavancin.
- Infusion related reactions - Intravenous infusions of oritavancin can cause reactions that resemble “red man syndrome”, including flushing of the upper body, urticaria, pruritis and/or rash. Infusion-associated reactions characterized by chest pain, chest discomfort, chills, tremor, back pain, neck pain, dyspnoea, hypoxia, abdominal pain and fever have been observed with the use of oritavancin, including after the administration of more than one dose of oritavancin (1200mg) during a single course of therapy.
- Concomitant use of warfarin - Oritavancin has been shown to artificially prolong prothrombin time (PT) and international normalised ratio (INR) for up to 12 hours, making the monitoring of the anticoagulation effect of warfarin unreliable up to 12 hours after an oritavancin dose.
- Clostridioides difficile - Antibacterial-associated colitis and pseudomembranous colitis have been reported for oritavancin and may range in severity from mild to life threatening diarrhoea.
- Osteomyelitis - In Phase 3 ABSSSI clinical trials, more cases of osteomyelitis were reported in the oritavancin-treated arm than in the vancomycin-treated arm.
- Abscess - In the Phase 3 clinical trials, slightly more cases of newly emergent abscesses were reported in the oritavancin-treated arm than in the vancomycin-treated arm (4.6% vs 3.4%, respectively).
- Limited clinical data - In the two major trials in ABSSSI the types of infections treated were confined to cellulitis, abscesses and wound infections only. Other types of infections have not been studied.

There is limited experience in clinical studies in patients with bacteraemia, peripheral vascular disease or neutropenia, in immunocompromised patients, in patients aged > 65 years and in infections due to *S. pyogenes*.

Special populations

Population pharmacokinetic analysis indicated that renal impairment had no clinically relevant effect on the exposure of oritavancin. No dedicated studies in dialysis patients have been conducted.

Undesirable effects

The most commonly reported adverse reactions (≥5%) were: nausea, hypersensitivity reactions, infusion site reactions, and headache. The most commonly reported serious adverse reaction was cellulitis (1.1%). The most common reported reasons for discontinuation were cellulitis (0.4%) and osteomyelitis (0.3%). Female patients had a higher reporting rate for adverse reactions than male patients.

System organ class	Frequency	Adverse Reactions
Infections and infestations		
	Common	Cellulitis, abscess (limb and subcutaneous)
	Uncommon	Osteomyelitis
Blood and lymphatic system disorders		
	Common	Anaemia
	Uncommon	Eosinophilia, thrombocytopenia
Immune system disorders		
	Uncommon	Hypersensitivity, anaphylactic reaction
	Unknown	Anaphylactic shock
Metabolism and nutrition disorders		
	Uncommon	Hypoglycaemia, hyperuricaemia
Nervous system disorders		
	Common	Headache, dizziness
	Rare	Tremor*
Cardiac disorders		
	Common	Tachycardia
Respiratory, thoracic and mediastinal disorders		
	Uncommon	Bronchospasm, wheezing, dyspnoea*
	Rare	Hypoxia*
Gastrointestinal disorders		
	Common	Nausea, vomiting, diarrhoea, constipation
	Uncommon	Abdominal pain*
Hepatobiliary disorders		
	Common	Liver function test abnormal (Alanine aminotransferase increased, Aspartate aminotransferase increased)
	Uncommon	Blood bilirubin increased
Skin and subcutaneous tissue disorders		
	Common	Urticaria, rash, pruritis
	Uncommon	Leucocytoclastic vasculitis, angioedema, erythema multiforme, flushing
Musculoskeletal and connective tissue disorders		
	Common	Myalgia
	Uncommon	Tenosynovitis

	Rare	Back pain*, neck pain*
General disorders and administration site conditions		
	Common	Infusion site reactions, including the following symptoms infusion site phlebitis, infusion site erythema, extravasation, induration, pruritis, rash, oedema peripheral
	Uncommon	Chest pain*, pyrexia*
	Rare	Red man syndrome, chest discomfort*, chills*

*These reactions may be infusion-related

Strengths and limitations of the evidence:

Strengths

- NICE consider oritavancin as an 'option' for ABBBSI when standard oral and intravenous antibiotics are not suitable.
- SMC has approved oritavancin for restricted use within NHS Scotland patients with confirmed or suspected methicillin-resistant Staphylococcus aureus (MRSA) infection who are eligible for early discharge.
- Both studies demonstrated non-inferiority for oritavancin vs. vancomycin.
- Oritavancin has demonstrated good activity against vancomycin-resistant enterococci (VRE) in vitro.
- ADRs appear to be mainly self-limiting, but there are concerns over increased prevalence of Osteomyelitis and of abscesses during oritavancin treatment, vs vancomycin. These have been noted on the SPC.

Limitations

- The study populations lacked diversity in patient characteristics and co-morbidities.
- The 2 main studies did not have UK participation, therefore may not be representative of UK MRSA prevalence or follow standard UK antimicrobial protocols.
- Oritavancin resistance data in the UK is limited.
- Comparative data to antimicrobials other than vancomycin is lacking. In particular data comparing oritavancin to teicoplanin.
- The SOLO I and SOLO II trials were not powered to detect non-inferiority in the MRSA subgroup.
- Oritavancin does not have any antibacterial properties that could be viewed as definite and proven advantages over other intravenous agents that have antibacterial spectra confined to certain Gram-positive organisms.

Summary of evidence on cost effectiveness:

Zinzi et al (2021)[16]

A cost-minimisation model considering adult patients with ABSSSI with suspected or confirmed methicillin-resistant Staphylococcus aureus (MRSA) infection, was developed based on publicly available NHS costs, practice guidelines for ABSSSI and clinical expert's opinion. Cost of treatment and treatment days were compared for oritavancin at early discharge to dalbavancin, teicoplanin, daptomycin and linezolid.

A cost-minimisation approach, which assumed equivalent efficacy for oritavancin and the model comparators, was adopted for this analysis.

All patients with ABSSSI included in the analysis were initiated on treatment with empiric therapy on day 0 to day 2 with either flucloxacillin (90% patients) or vancomycin (10% patients) as inpatient treatment. On day 3, it was assumed that 100% of the patients had confirmed MRSA infection and were switched to vancomycin. On day 4, it was assumed that 100% patients were eligible for ED to outpatient treatment with the following therapeutic treatment options: single dose IV oritavancin, dalbavancin (either as a single 1500 mg dose or two doses: 1000 mg initial dose, followed by 500 mg a week later), OPAT teicoplanin, OPAT daptomycin, or oral linezolid until day 10. On day 10, all cured OPAT patients were discharged from clinical care. However, if clinical cure was not confirmed, patients were deemed as treatment failures and a 10-day course of inpatient rescue therapy with IV linezolid was initiated. It was also assumed that a subset of

patients clinically cured after first-line therapy may experience relapse requiring hospitalisation, these relapses were associated with a 10-day inpatient rescue therapy.

The total medication cost for oritavancin (£1751) was lower in comparison to dalbavancin (£1927), whilst it was higher than teicoplanin (£302), daptomycin (£611), and linezolid (£349).

With respect to treatment duration, oritavancin was associated with a reduction in treatment days versus all comparators, ranging from 0.8 (versus dalbavancin) to 5.0 days (versus teicoplanin, daptomycin and linezolid).

Oritavancin was the dominant comparator in contrast to dalbavancin, with reduced costs and treatment days. Whereas, considering the reduction in treatment days, it was estimated that oritavancin was associated with a small incremental cost per treatment day avoided in comparison to teicoplanin, daptomycin and linezolid (£89, £27, £287, respectively).

Mortality and quality of life were not considered in the CMM due to the short time horizon of the CMM. Adverse events were not considered in the CMM, due to similar safety profiles between comparators. Costs for the additional components needed for drug infusions (such as glucose and sodium chloride) were not considered.

Wu C et al (2015)[17]

For a UK hospital treating 100 SSTI patients per year eligible for IV antibiotics, using oritavancin conservatively (3.6% of patients) would decrease total annual cost by £2,922.52. Increased pharmaceutical costs (£6,111.21) were offset by reductions in drug administration costs (-£5,531.13) and hospitalization/OPAT costs (-£3,379.48). Inpatient and outpatient days of treatment were reduced by 8.2 and 16.4 days, respectively.

Using oritavancin conservatively in moderate-to-severe SSTI patients is estimated to reduce costs by £29.23/patient by shifting patient care to the outpatient setting, allowing for early discharge, and reducing hospitalisation and drug administration costs.

Prescribing and risk management issues:

- No data is available on cross-reactivity between oritavancin and other glycopeptides, including vancomycin. Before using oritavancin it is important to inquire carefully about previous hypersensitivity reactions to glycopeptides (e.g. vancomycin, telavancin). Due to the possibility of cross-hypersensitivity, there should be careful monitoring of patients with any history of glycopeptide hypersensitivity during and after the infusion.
- Oritavancin has been shown to interfere with certain laboratory coagulation tests, it may artificially prolong:
  - aPTT for up to 120 hours,
  - PT and INR for up to 12 hours,
  - Activated Clotting Time (ACT) for up to 24 hours,
  - Silica Clot Time (SCT) for up to 18 hours, and
  - Dilute Russell's Viper Venom Test (DRVVT) for up to 72 hours.
- Tenkasi should be prepared under aseptic techniques in a pharmacy.

Commissioning considerations:

Innovation, need and equity implications of the intervention:

Specialist Pharmacy Service

A single dose alternative to antibiotics such as aztreonam, cefazolin, dalbavancin, daptomycin, delafloxacin, linezolid, tedizolid, tigecycline and vancomycin which are given daily. This could support management in other settings. Antibiotic resistance is increasingly common in acute bacterial skin and skin structure infections (ABSSSI) and this offers an alternative when adherence to other therapy is likely to be poor.

Unlike vancomycin and linezolid, it does not require monitoring (e.g. of blood levels, renal function, full blood counts) or dose adjustment, and has no significant drug interactions.[5]

Financial implications of the intervention:

Oritavancin

1,200 mg administered as a single dose by intravenous infusion over 3 hours.

NHS indicative price = **£1500** for 1 dose (3 x 400mg vials) As per BNF Oct 2022

Potential additional costs: Additional components for drug infusion including infusion fluid, hospital time and facilities, additional oral/IV antibiotics based on cultures.

Teicoplanin

For example: East Lancashire Hospitals NHS Trust: Cellulitis – OPAT[18]

Loading: Teicoplanin 1g-1.2g daily for 3 days (body weight and renal function dependent)

Maintenance: 600mg-1g every 24h-72h

Therefore, minimum of 4 infusions required.

4 infusions incl loading = approx **£66.96 - £84.45 drug cost** Prices based on drug tariff Nov 2022

7 infusions incl loading = approx. **£100.71 - £140.16 drug cost**

Potential additional costs: Additional components for drug infusion including infusion fluid, hospital time and facilities, additional oral/IV antibiotics based on cultures, **OPAT costs, renal monitoring, trough levels for extended courses.**

OPAT costs

According to the National Schedule of NHS costs[19], a non-consultant led, clinical microbiology, non-admitted face to face attendance has a national average unit cost of £115.59.

If this is added onto the approximate cost of each infusion (based on the ELHT regemin), the approximate maximum drug plus OPAT cost for teicoplanin is:

4 infusions = **£546.81**

7 infusions = **£949.29**

Service Impact Issues Identified:

Potential to reduce nursing time.

Compliance with therapy could be improved, particularly in specific patient groups which may struggle with access to therapy. E.g. the homeless, patient's in isolated housing, patients with caring responsibilities.

Removes the need to maintain venous access.

Equality and Inclusion Issues Identified:

May improve access to therapy for some patients.

Cross Border Issues Identified:

The **Pan Mersey APC** do not have oritavancin in their formulary.

The **Greater Manchester Medicines Management Group** (GMMMG) do not have oritavancin in their

formulary.
Legal Issues Identified:
None identified.
Media/ Public Interest:
None identified.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

References

[1] Electronic Medicines Compendium, "Summary of Product Characteristics Tenkasi 400 mg powder for concentrate for solution for infusion", A. Menarini Farmaceutica Internazionale SRL, Apr 2022 [Online]. Available: https://www.medicines.org.uk/emc/product/13554

[2] British National Formulary, "Oritavancin" [Online]. Available: https://bnf.nice.org.uk/drugs/oritavancin/#other-drugs-in-class [Accessed 24 October 2022]

[3] National Institute for Health and Care Excellence, "NG141 Cellulitis and erysipelas: antimicrobial prescribing visual summary", 2019 [Online]. Available: https://www.nice.org.uk/guidance/ng141/resources/visual-summary-pdf-6908401837

[4] National Institute for Health and Care Excellence and Public Health England, "Summary of antimicrobial prescribing guidance – managing common infections", 2022 [Online]. Available: https://www.bnf.org/wp-content/uploads/2022/03/summary-antimicrobial-prescribing-guidance_mar-22_v0.2.pdf

[5] National Institute for Health and Care Excellence, "Antimicrobial prescribing: oritavancin for acute bacterial skin and skin structure infections", 2022 [Online]. Available: https://www.nice.org.uk/advice/es39/resources/antimicrobial-prescribing-oritavancin-for-acute-bacterial-skin-and-skin-structure-infections-pdf-1158244672453

[6] Shah M et al, "Acute bacterial skin and skin structure infections: current perspective", *Indian Journal of Dermatology*, vol. 56(5), pp 510-2, 2011

[7] Liu et al, "Antibacterial activity of recently approved antibiotics against methicillin-resistant Staphylococcus aureus (MRSA) strains: A systematic review and meta-analysis", *Annals of Clinical Microbiology and Antimicrobials*, vol. 21, 2022

[8] Specialist Pharmacy Service, "Oritavancin", 2015

[9] Scottish Medicines Consortium, "oritavancin (Tenkasi)", 2022. [Online] Available: https://www.scottishmedicines.org.uk/medicines-advice/oritavancin-tenkasi-resub-smc2285/

[10] European Medicines Agency, "Tenkasi (previously Orbactiv): EPAR – Public assessment report", 2015

[11] Corey GR et al, "Single-dose oritavancin in the treatment of acute bacterial skin infections", *New England Journal of Medicine*, vol. 370, pp 2180–90, 2014

[12] Corey GR et al, "Single-dose oritavancin versus 7–10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study", *Clinical Infectious Diseases*, vol. 60, pp 254–62, 2015

[13] Brown et al, "Treatment of methicillin-resistant Staphylococcus aureus (MRSA): updated guidelines from the UK", *Journal of Antimicrobial Chemotherapy – Antimicrobial Resistance*, 2021

[14] Estrada et al, "The Real-World Economic and Clinical Management of Adult Patients with Skin and Soft Tissue Infections (SSTIs) with Oritavancin: Data from Two Multicenter Observational Cohort Studies", *Drugs - Real World Outcomes,* vol 7(1), pp 6-12, 2020

[15] Saravolatz et al, "Oritavancin: A Long-Half-Life Lipoglycopeptide", *Clinical Infectious Diseases*, vol. 61(4), pp 627–32, 2015

[16] Zinzi et al, "Cost-minimisation analysis of oritavancin for the treatment of acute bacterial skin and skin structure infections from a United Kingdom perspective", The European Journal of Health Economics, 2021

[17] Wu C et al. "Use of Oritavancin for the Treatment of Skin and soft Tissue Infections: A UK Hospital Budget Impact Analysis", *Value in Health [ISPOR]*, vol. 18(3), pp 233, abstract PIN32, 2015

[18] East Lancashire Hospitals NHS Trust, "Cellulitis – OPAT" [Online]. Available: https://viewer.microguide.global/elht/adult?https://viewer.microguide.global/elht/adult#content,c2acef1a-d988-4d10-807a-478b823b4fac

[19] NHS England, "National Cost Collection for the NHS", 2020/21 [Online]. Available: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/#ncc1819