NICE National Institute for Health and Care Excellence

Antimicrobial prescribing: oritavancin for acute bacterial skin and skin structure infection

Evidence review

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This evidence review sets out the best available evidence on oritavancin for treating acute bacterial skin and skin structure infections in adults. It should be read in conjunction with the evidence summary, which gives the likely place in therapy and factors for decision making.

Disclaimer

The content of this evidence review was up to date in February 2022. See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

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Background

Acute bacterial skin and skin structure infections (ABSSSI) are common bacterial infections. They may require systemic antibiotics, surgical management and hospitalisation. ABSSSIs include cellulitis, erysipelas, wound infections, major cutaneous abscesses and burn infections (European public assessment report [EPAR] on oritavancin).

The management of ABSSSI depends on the clinical presentation and the severity of the infection. The NICE antimicrobial prescribing guideline on cellulitis and erysipelas advises that the severity of symptoms, site of infection, risk of uncommon pathogens, any microbiological results and meticillin-resistant *Staphylococcus aureus* (MRSA) status should be taken into account when choosing an antibiotic. There are also NICE guidelines on surgical site infections and leg ulcer infection. An evidence summary on delafloxacin for acute bacterial skin and skin structure infections was published in January 2021.

The most common bacteria associated with ABSSSI is *Staphylococcus aureus* (*S. aureus*). Resistance has been reported in S. *aureus*, such as MRSA, where choice of treatment can be challenging (EPAR on oritavancin).

The English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report (2020 to 2021) states that S. *aureus* was the second most common cause of blood stream infection in 2016 to 2020. There was an incidence of 21.8 per 100,000 population in 2016, increasing to around 23 per 100,000 in 2017 to 2019, and declining to 21.4 per 100,000 in 2020. This decrease is thought to be due to pandemic-associated reduction in person-to-person contact. The Public Health England Annual epidemiological commentary (2020 to 2021) reports that from April 2020 to March 2021, 5.6% of S. *aureus* bacteraemia reports were caused by MRSA. This was a decrease of 14.7% from April 2019 to March 2020. Both reports do not include data specifically for ABSSSI.

The NICE antimicrobial prescribing guideline on cellulitis and erysipelas recommends that, if MRSA infection is suspected or confirmed, combination therapy including either vancomycin, teicoplanin or linezolid should be used.

Product overview

Mode of action

Oritavancin is a glycopeptide antibiotic with 3 mechanisms of action, including inhibition of cell wall biosynthesis and disruption of bacterial membrane integrity. It is active against gram-positive bacteria only (summary of product characteristics [SPC] for oritavancin).

Regulatory status

Oritavancin (Tenkasi) has a marketing authorisation for treating ABSSSI in adults (SPC for oritavancin). It was launched in the UK in April 2022.

Dosing information

Oritavancin is available as a 400 mg powder for concentrate for solution for infusion. The recommended dosage is 1,200 mg given as a single dose by intravenous infusion over 3 hours. Oritavancin has a prolonged half-life (approximately 245 hours) allowing for a single dose treatment course (SPC for oritavancin).

Antimicrobial resistance

Gram-negative organisms are resistant to all glycopeptides, including oritavancin. Resistance to oritavancin was seen *in vitro* in vancomycin-resistant isolates of *S. aureus*. There is no known cross-resistance between oritavancin and non-glycopeptide classes of antibiotics (SPC for oritavancin).

Objective

This evidence review aims to review the best available evidence on the effectiveness and safety of oritavancin for treating ABSSSI in adults.

Review questions

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review questions for this evidence review are:

1. What is the effectiveness of oritavancin for the treatment of ABSSSI in adults?

2. What is the safety of oritavancin for the treatment of ABSSSI in adults?

Summary of included studies

A literature search for oritavancin for treating ABSSSI identified 402 references (see appendix E for full details). These references were screened using their titles and abstracts and 11 full text references were obtained and assessed for relevance.

Two studies are included in this evidence summary. A summary of the included studies is shown in appendix B. Quality assessment of the included studies is in appendix C.

The 2 studies in the evidence review are phase 3, double-blind randomised controlled non-inferiority trials of identical design. Corey et al. 2014 (n=968) and Corey et al. 2015 (n=1,019) both compared oritavancin with vancomycin to treat ABSSSI in adults with cellulitis or erysipelas, wound infection or major cutaneous abscess. The duration of oritavancin was 1 day (a single dose over 3 hours) and the duration of vancomycin was 7 to 10 days.

Nine studies were excluded. Details of these excluded studies are in appendix F.

Effectiveness and safety

Full details of the results are in appendix D.

Review question 1: What is the effectiveness of oritavancin for the treatment of ABSSSI in adults?

Clinical response

Both studies found that oritavancin was non-inferior to vancomycin for the primary end point, early clinical response after 48 to 72 hours after treatment. Oritavancin was also non-inferior to vancomycin for the key secondary end points of investigator-assessed clinical cure 7 to 14 days after treatment finished, and 20% or more reduction in lesion size after 48 to 72 hours of administration. Investigator-assessed clinical cure 7 to 14 days after treatment finished was the primary end point for the European Medicines Agency (EMA) submission (EPAR on oritavancin).

Early clinical response was a composite outcome including cessation of spreading or reduction in the size of baseline lesion, absence of fever and no rescue antibacterial agent given. Success was defined if all 3 components were met, as defined by the US Food and Drug Administration (FDA). Corey et al. 2014 found that 82.3% of people in the oritavancin arm and 78.9% of people in the vancomycin arm met the early clinical response (difference 3.4%, 95% confidence interval [CI] -1.6% to 8.4%, non-inferiority margin of -10% met). Corey et al. 2015 found that 80.1% of people in the oritavancin arm and 82.9% of people in the vancomycin arm met the primary end point (difference -2.7%, 95% CI -7.5% to 2.0%, non-inferiority margin of -10% met).

Investigator-assessed clinical cure was defined as complete resolution of signs and symptoms 7 to 14 days after treatment finished. Corey et al. 2014 reported that 79.6% of people in the oritavancin arm and 80.0% of people in the vancomycin arm met this end point (difference -0.4%, 95% CI -5.5% to 4.7%, non-inferiority margin of-10% met). Corey et al. 2015 reported that 82.7% of people in the oritavancin arm and 80.5% of people in the vancomycin arm met this end point (difference 2.2%, 95% CI -2.6% to 7.0%, non-inferiority margin of -10% met).

Corey et al. 2014 found that the lesion size reduced by 20% or more in 86.9% of people in the oritavancin arm and 82.9% of people in the vancomycin arm (difference 4.1%, 95% CI -0.5% to 8.6%, non-inferiority margin of -10% met). Corey et al. 2015 found that the lesion size reduced by 20% or more in 85.9% of people in the oritavancin arm and 85.3% of people in the vancomycin arm (difference 0.6%, 95% CI -3.7% to 5.0%, non-inferiority margin of -10% met).

Clinical response on baseline pathogen

The most common pathogen detected at baseline was *S. aureus*; including MRSA. Within the population evaluated microbiologically for S. *aureus*, Corey et al. 2014 (n=430) identified 352 (81.9%) people with S. *aureus* at baseline. Of these, 164 (46.6%) people had MRSA and 188 (53.4%) had meticillin-susceptible *Staphylococcus aureus* (MSSA). Within the population evaluated microbiologically for S. *aureus*, Corey et al. 2015 (n=508) identified 427 (84.1%) people with *S. aureus* at baseline, of these 164 (38.4%) people had MRSA and 263 (61.6%) people had MSSA.

Both papers reported outcomes for the primary end point, early clinical response, for the subpopulation of people with MRSA at baseline. Corey et al. 2014 found that 80.8% of people with MRSA in the oritavancin arm and 80.0% of people with MRSA in the vancomycin arm met the primary end point (difference 0.8%, 95% CI −10.1 to 11.7). Corey et al. 2015 found that 82.0% of people with MRSA in the oritavancin arm and 81.2% of people with MRSA in the vancomycin arm met the primary end point (difference 0.8%, 95% CI -9.9 to 11.5).

Review question 2: What is the safety of oritavancin for the treatment of ABSSSI in adults?

In Corey et al. 2014 and Corey et al. 2015, approximately 60% and 50% of people in both arms reported at least 1 treatment-emergent adverse event, respectively. The follow up in both studies was 60 days. Treatment-related adverse events were seen in 22.8% of people in the oritavancin arm and 31.4% of people in the vancomycin arm in Corey et al. 2014, and 21.7% of people in the oritavancin arm and 25.5% of people in the vancomycin arm in Corey et al. 2015. The most frequently reported adverse events in the oritavancin arm in both studies were nausea, headache and vomiting. No statistical analyses were presented for safety data.

Corey et al. 2014, reported serious adverse events in 7.4% of people in the oritavancin arm and 7.3% of people in the vancomycin arm; and Corey et al. 2015, reported serious adverse events in 4.4% of people in the oritavancin arm and 4.6% of people in the vancomycin arm. The total number of reported deaths in both studies were 2 people in the oritavancin arms and 3 people in the vancomycin arms. The causes of death were sepsis and electromechanical dissociation in the oritavancin group, and septic shock, acute myocardial infarction and dementia with Parkinsonism in the vancomycin group. None of the deaths were considered related to study treatment.

The SPC for oritavancin states that the most commonly reported adverse reactions were nausea, hypersensitivity reactions, infusion site reactions and headache. The most commonly reported serious adverse reaction was cellulitis. The most common reported reasons for discontinuation were cellulitis and osteomyelitis.

The EPAR on oritavancin concluded that, from the phase 3 studies, oritavancin had a similar safety profile to vancomycin. From a pooled analysis of 22 phase 1, 2 and 3 clinical studies the EPAR reported that the incidence in vestibular toxicity and renal adverse events was similar between the oritavancin and vancomycin groups. However it also highlighted some safety concerns; in particular, increased reports of osteomyelitis and abscesses with oritavancin. The EPAR concluded that this may suggest that oritavancin could have some detrimental effect on the migration or function of phagocytic cells in deep seated tissues despite the fact that efficacy against ABSSSI was comparable to that of vancomycin and *in vitro* studies showed macrophages to retain functionality. Overall the EMA considered the risk-benefit balance to be favourable with a risk management plan to assess adverse events of osteomyelitis and abscesses and adequate warnings in the SPC. Suspected adverse reactions associated with oritavancin should be reported via the Yellow Card Scheme.

Regarding *Clostridioides difficile*-associated diarrhoea, the EPAR on oritavancin outlines that antibacterial-associated colitis and pseudomembranous colitis have been reported with oritavancin and may range in severity from mild to life-threatening diarrhoea.

See the SPC for further information on contraindications, warnings and interactions.

Limitations of the evidence

In both studies the people enrolled were predominately male, under 65 years old and of white ethnicity. In Corey et al. 2014 and Corey et al. 2015 respectively, 63.1% and 67.8% of people were male; 91.1% and 92.2% of people were under 65 years old and 57.5% and 70.8% of people were white. 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 results may not be representative for some populations.

In line with EMA and FDA guidance on evaluating medicines for ABSSSI, only people with cellulitis or erysipelas, abscesses and wound infections were included, and all other infections were excluded. The people in the studies had cellulitis

(49.9% and 40.0%), wound infections (20.6% and 36.5%) or abscesses (29.5% and 32.5%), in Corey et al. 2014 and Corey et al. 2015 (respectively). Further studies would be required to assess the effectiveness of oritavancin in other infections such as bacteraemia, osteomyelitis, prosthetic-joint infections and infections due to *Streptococcus pyogenes* (S. *pyogenes*).

The baseline lesion size and infection type across both treatment groups was relatively similar in both studies. The median lesion area was between 225 cm^2 to 248 cm^2 in Corey et al. 2014 and between 287 cm^2 to 309 cm^2 in Corey et al. 2015 and people had at least 2 signs of systemic infection, indicating that the infections were severe. Corey et al. 2014 and Corey et al. 2015 did not report how many people received antibiotics prior to enrolling into the study.

In both studies, vancomycin was used as the comparator, each study site could choose to administer a dose of either 1 g or 15 mg/kg every 12 hours. This was managed by a designated unblinded member of the team at each study site. The lack of standardised dosing in the vancomycin arm may have impacted the results. However, the EPAR notes that the cure rates with vancomycin were within the expected range. Oritavancin has not been compared with other antibiotics, such as dalbavancin, in phase 3 studies.

Aztreonam or metronidazole were allowed for people with mixed infections (where gram-negative or anaerobic bacteria were suspected respectively) in both arms of both studies (99 [10.4%] of people received aztreonam and 32 [3.4%] of people received metronidazole in Corey et al. 2014 and 91 [9.1%] of people received aztreonam and 54 [5.4%] of people received metronidazole in Corey et al. 2015).

The NICE antimicrobial prescribing guideline on cellulitis and erysipelas recommends vancomycin as an option only when MRSA is suspected or confirmed. Aztreonam and metronidazole are not standard treatment options for severe infections in the NICE guideline, although the guidance does state other antibiotics may be appropriate based on microbiological results and specialist advice. Within the population evaluated microbiologically who had confirmed S. *aureus*, Corey et al. 2014 (n=352) identified 164 (46.6%) people had MRSA and Corey et al. 2015 (n=427) identified 164 (38.4%) people had MRSA. Both studies were multicentre and

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

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 Corey et al. 2014 and Corey et al. 2015, people in the vancomycin arm were not reviewed at 48 to 72 hours for consideration of oral antibiotics. Oritavancin has a prolonged half-life (approximately 245 hours) allowing for a single dose.

Person-centred factors

Oritavancin is given intravenously as a single infusion over 3 hours. It is likely to be prescribed in a hospital setting. Specialists who commentated on this evidence review highlighted that in practice oritavancin is likely to be provided in an ambulatory care setting or through outpatient parental antimicrobial therapy for people with severe skin infections. Oritavancin has a marketing authorisation for treating adults only and there is no requirement to adjust the dose for age, weight, or mild to moderate renal function. Oritavancin has not been evaluated in people with severe renal impairment. Therapeutic drug monitoring is also not required, which may mean fewer blood tests than for some other intravenous antibiotics used for people with ABSSSI (SPC for oritavancin).

Oritavancin offers a single intravenous treatment which may be preferable in some circumstances to other antibiotics used for ABSSSI, which are given for several days, often multiple times a day.

Resource implications

Oritavancin is given intravenously as a single infusion over 3 hours. The cost of a single infusion at a dose of 1,200 mg (3 vials) is £1,500 (see MIMS, May 2022). This cost is for the medicine only and does not include any associated costs related to antibiotic administration.

The recommended treatment duration in the NICE antimicrobial prescribing guideline on cellulitis and erysipelas is 7 days for severe infection with intravenous antibiotics reviewed after 48 hours for consideration to switch to oral antibiotics. A wide range of antibiotics, alone or in combination, are used for treating ABSSSI, depending on the severity of symptoms, site of infection, risk of uncommon pathogens, any microbiological results and MRSA status. Examples of antibiotics that might be used for severe infection include flucloxacillin, cephalosporins, extended-spectrum penicillins with beta-lactamase inhibitors, clindamycin and, in MRSA infection, vancomycin, teicoplanin or linezolid.

The manufacturer of oritavancin (Menarini) anticipates the uptake of oritavancin will be approximately 100 patients in year 1 rising to approximately 600 patients in year 3.

References

Corey, G Ralph et al. (2014) Single-dose oritavancin in the treatment of acute bacterial skin infections. The New England journal of medicine vol. 370 (23): 2180-90

Corey, G Ralph et al. (2015) 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 (2): 254-62

Development of the evidence review

Process

The evidence summary: process guide sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers

Details of expert advisers and any declarations of interest

Name, job title and organisation	Declaration of interest
TangNGee Shim, Consultant Dermatologist, University Hospitals Coventry & Warwickshire NHS Trust	Paid to attend to speak at a British Association for Sexual Health & HIV course, British Association of Dermatologist Virtual Meeting, an American Academy Dermatology Virtual Meeting and an Abbvie UK Virtual Advisory Board (financial interests in June 2020 to November 2021) Private practice in the BMI Meriden Hospital, and Spire Southbank Hospital (Financial interest July 2019 – ongoing)
Natasha Ratnaraja, Consultant Microbiologist, University Hospitals Coventry and Warwickshire NHS Trust	Microbiologist for BMI Meriden healthcare providing clinical advice (Financial interest October 2018 – ongoing) Council member British Infection Association (Non-financial interest September 2016 – ongoing) Reviewer for NICE (Non-financial interest October 2019 – ongoing) Deputy Chair Medical Microbiology & Virology SAC, RCPath (Non-financial interest April 2021-ongoing) Member of RCPath COVID Action Group (Non-financial interest- November 2020- ongoing) BIA representative on SMI bacteriology working group (Non-financial interest June 2021-ongoing) Affiliate member of ID CRG (Non-financial interest January 2021- ongoing)
Philippa Moore, Consultant Medical Microbiologist, Gloucestershire Hospitals NHS Foundation Trust	Clinical Microbiology Consultancy Limited – director, private company offering advice to local Nuffield hospitals and Pura Diagnostics Ltd (Financial interest 2011 – ongoing) Consultancy role to Tillotts Pharma UK Ltd (Financial interest- July 2021-November 2021) South West representative on Clinical Services Committee of British Infection Association (Non-financial interest- 2020-ongoing)
Colin Brown, Deputy Director (Interim), Healthcare-associated Infections and Antimicrobial Resistance, National Infection Service, UK Health Security Agency	Microbiology support to a private charitable hospital with onsite hospice (Financial interest- January 2020- ongoing) Ad hoc one-off market research advisory (Financial interest- 2012-ongoing) Occasional contact with companies promoting novel antimicrobial therapies through role with AMRHAI (antimicrobial resistance and healthcare associated infections) as the national reference laboratory for investigating AMR in healthcare-associated bacteria (Non-financial interest- April 2019- ongoing)

Name, job title and organisation	Declaration of interest
	Attend Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI) and the Antimicrobial Programme Board on behalf of Public Health England (Non-financial interest- April 2019- ongoing)
Alicia Demirjian, Consultant Epidemiologist, UK Health Security Agency; Consultant in paediatric infectious diseases, Evelina London Children's Hospital	Lead of the UK Paediatric Antimicrobial Stewardship network (Non-financial interest- 2019-ongoing)

Appendices

Appendix A: PICO table

PICO table

Criteria	Details
P – Population and indication	Adults aged 18 years and over who have acute bacterial skin and skin structure infection (ABSSSI)
I – Intervention	Oritavancin (brand name: Tenkasi, previously Orbactiv) 400 mg powder for concentrate for solution for infusion Dose for ABSSSI: 1,200 mg as a single dose by IV infusion over 3 hours
C – Comparator(s)	Any comparator
O – Outcomes	Clinical response Microbiological response Adverse events
Inclusion criteria	-
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials If no higher-level quality evidence is found, observational studies including case series can be considered
Language	English
Patients	Human studies only
Age	Adults 18 years and over
Date limits	None
Exclusion criteria	-
Publication type	Pre-prints prior to peer review, letters, conference abstracts or studies that have not been published in full
Study design	Case reports

Appendix B: Summary of included studies

Summary of included studies

Study	Number of participants	Population	Intervention	Comparison	Outcomes
Corey et al. 2014 Double-blind RCT non-inferiority study	n=968 (follow up 60 days)	Adults aged 18 years or over with diagnosis of ABSSSI suspected or proven to be caused by a gram-positive pathogen and expected to need at least 7 days of IV treatment.	A single 1200 mg IV dose of oritavancin followed by a placebo IV infusion every 12 hours for 7 to 10 days (n=483)	Vancomycin 1 g or 15 mg/kg IV every 12 hours for 7 to 10 days (n=485)	Primary efficacy outcome: early clinical response at the ECE visit (48 to 72 hours after initiation) Key secondary efficacy outcome: investigator-assessed clinical cure at PTE visit (7 to 14 days after treatment ended) Other secondary outcomes: lesion size reduction ≥20% from baseline at ECE visit and adverse events
Corey et al. 2015 Double-blind RCT non-inferiority study	n=1,019 (follow up 60 days)	Adults aged 18 years or over with diagnosis of ABSSSI suspected or proven to be caused by a gram-positive pathogen and expected to need at least 7 days of IV therapy.	A single 1,200 mg IV dose of oritavancin followed by a placebo IV infusion every 12 hours for 7 to 10 days (n=509)	Vancomycin 1 g or 15 mg/kg IV every 12 hours for 7 to 10 days (n=510)	Primary efficacy outcome: early clinical response at the ECE visit (48 to 72 hours after initiation) Key secondary efficacy outcome: investigator-assessed clinical cure at PTE visit (7 to 14 days after treatment ended) Other secondary outcomes: lesion size reduction ≥20% from baseline at ECE visit and adverse events

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; IV, intravenous; ECE, early clinical evaluation; PTE, post-therapy evaluation; RCT, randomised controlled trial

In both studies, the diagnosis of ABSSSI required the presence of wound infection (either traumatic or surgical in origin), cellulitis, erysipelas, or a major cutaneous abscess, with each lesion surrounded by erythema, oedema, or an induration of at least 75 cm^2 and at least 2 signs of systemic infection.

Both studies allowed aztreonam and metronidazole for gram-negative and anaerobic coverage respectively.

Early clinical response was a composite outcome defined by the US Food and Drug Administration of the following: cessation of spreading or reduction in the size of baseline lesion, absence of fever and no rescue antibacterial agent given. Success was defined if all 3 components were met. If 1 or more of the following occurred, failure was documented: death (all-cause mortality) during the first 72 hours, fever defined as at least one oral temperature reading of 37.7°C or above between 48 and 72 hours, spreading of lesion size at 48 to 72 hours compared to baseline, requirement for rescue antibiotics during the first 72 hours or an unplanned surgical procedure during the first 72 hours (EPAR on oritavancin).

Investigator-assessed clinical cure at PTE was defined as complete or nearly complete resolution of baseline signs and symptoms of the infection and confirmation that no further antibiotics are required 7 to 14 days after treatment finished (Corey et al. 2014).

Appendix C: Quality assessment of included studies

Quality assessment of Corey et al. 2014

Question	Corey et al. (2014)
Domain 1: Risk of bias arising from the randomisation process	-
1.1 Was the allocation sequence random?	Yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Risk of bias judgement	Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	-
2.1. Were participants aware of their assigned intervention during the trial?	No
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably no
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	-
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	-
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	-
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	-
Risk of bias judgement	Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	-
2.1. Were participants aware of their assigned intervention during the trial?	No
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably no
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	-
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	Probably no

Question	Corey et al. (2014)
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	Probably no
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	-
Risk of bias judgement	Low
Domain 3: Missing outcome data	-
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	-
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	-
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	-
Risk of bias judgement	Low
Domain 4: Risk of bias in measurement of the outcome	-
4.1 Was the method of measuring the outcome inappropriate?	No
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Probably no
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	-
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	-
Risk of bias judgement	Low
Domain 5: Risk of bias in selection of the reported result	-
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis?	Yes
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No
Risk of bias judgement	Low
Overall risk of bias judgement	Low

Checklist used: Cochrane risk of bias 2 tool

Abbreviations: Y, Yes; PY, Probably yes; PN, Probably no; N, No; NI, No information.

Quality assessment of Corey et al. 2015

Question	Corey et al. (2015)
Domain 1: Risk of bias arising from the randomisation process	-
1.1 Was the allocation sequence random?	Probably yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Probably yes
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Risk of bias judgement	Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	-
2.1. Were participants aware of their assigned intervention during the trial?	Probably no
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably no
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	-
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	-
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	-
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	-
Risk of bias judgement	Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	-
2.1. Were participants aware of their assigned intervention during the trial?	Probably no
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably no
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	-

Question	Corey et al. (2015)
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	Probably no
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	Probably no
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	-
Risk of bias judgement	Low
Domain 3: Missing outcome data	-
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	-
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	-
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	-
Risk of bias judgement	Low
Domain 4: Risk of bias in measurement of the outcome	-
4.1 Was the method of measuring the outcome inappropriate?	No
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Probably no
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	-
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	-
Risk of bias judgement	Low
Domain 5: Risk of bias in selection of the reported result	-
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis?	Yes
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No

Question	Corey et al. (2015)
Risk of bias judgement	Low
Overall risk of bias judgement	Low

Checklist used: Cochrane risk of bias 2 tool.

Abbreviations: Y, Yes; PY, Probably yes; PN, Probably no; N, No; NI, No information.

Appendix D: Results tables

Results table for Corey et al. 2014

Outcome	Oritivancin IV	Vancomycin IV	Analysis
Primary outcome	**n=475**	**n=479**	**-**
Early clinical response at the ECE (mITT population)	391/475 (82.3%)	378/479 (78.9%)	Treatment difference 3.4% (95% CI -1.6% to 8.4% [non-inferiority margin met])
Secondary outcomes	**n=475**	**n=479**	**-**
Investigator-assessed clinical cure at PTE (mITT population)	378/475 (79.6%)	383/479 (80.0%)	Treatment difference -0.4% (95% CI -5.5% to 4.7% [non-inferiority margin met])
Lesion size reduction of 20% or more at ECE (mITT population)	413/475 (86.9%)	397/479 (82.9%)	Treatment difference 4.1% (95% CI -0.5% to 8.6% [non-inferiority margin met])
Early clinical response at the ECE (CE population)	344/394 (87.3%)	342/397 (86.1%)	Treatment difference 1.2% (95% CI -3.6% to 5.9% [non-inferiority margin met])
Investigator-assessed clinical cure at PTE (CE population)	357/394 (90.6%)	352/397 (88.7%)	Treatment difference 1.9% (95% CI -2.3% to 6.2% [non-inferiority margin met])
Lesion size reduction of 20% or more at ECE (CE population)	362/394 (91.9%)	370/397 (93.2%)	Treatment difference -1.3% (95% CI -5.0% to 2.3% [non-inferiority margin met])
Early clinical response at ECE (people with MRSA in the ME population)	84/104 (80.8%)	80/100 (80.0%)	Treatment difference 0.8% (95% CI -10.1% to 11.7%)
Investigator-assessed clinical cure at PTE (people with MRSA in the ME population)	86/104 (82.7%)	83/100 (83.0%)	Treatment difference -0.3% (95% CI -10.7% to 10.0%)
Lesion size reduction of 20% or more at ECE (people with MRSA in the ME population)	94/104 (90.4%)	84/100 (84.0%)	Treatment difference 6.4% (95% CI -2.8% to 15.5%)

Early clinical response at ECE (people with MSSA in the ME population)	96/116 (82.8%)	92/110 (83.6%)	Treatment difference -0.9% (95% CI -10.6% to 8.9%)
Investigator-assessed clinical cure at PTE (people with MSSA in the ME population)	89/116 (76.7%)	88/110 (80.0%)	Treatment difference -3.3% (95% CI -14.0% to 7.4%)
Lesion size reduction of 20% or more at ECE (people with MSSA in the ME)	98/116 (84.5%)	94/110 (85.5%)	Treatment difference -1.0% (95% CI -10.3% to 8.3%)
Safety outcomes	**n=473**	**n=481**	**-**
At least 1 treatment-emergent adverse event	284/473 (60.0%)	307/481 (63.8%)	No statistical analysis reported
Serious adverse events	35/473 (7.4%)	35/481 (7.3%)	No statistical analysis reported
Deaths	1/473 (0.2%)	2/481 (0.4%)	No statistical analysis reported
Treatment-related adverse events	108/473 (22.8%)	151/481 (31.4%)	No statistical analysis reported
Treatment-emergent adverse events resulting in treatment discontinuation	18/473 (3.8%)	28/481 (5.8%)	No statistical analysis reported
Nausea	52/473 (11.0%)	43/481 (8.9%)	No statistical analysis reported
Headache	34/473 (7.2%)	38/481 (7.9%)	No statistical analysis reported
Vomiting	23/472 (4.9%)	18/481 (3.7%)	No statistical analysis reported
Abscess on limb	13/473 (2.7%)	5/481 (1.0%)	No statistical analysis reported
Osteomyelitis	1/473 (0.2%)	1/481 (0.2%)	Reported from the EPAR

Abbreviations: IV, intravenous; CI, confidence interval; mITT, modified intent-to-treat; CE, clinically evaluable; ECE, early clinical evaluation; ME, Microbiologically evaluable; MRSA, meticillin-resistant *Staphylococcus aureus*; MSSA, meticillin-susceptible *Staphylococcus aureus*; and PTE, post-therapy evaluation

The modified intent-to-treat (mITT) population included all randomised participants who received either oritavancin or vancomycin. Non-inferiority was concluded if the lower bound of the 2-sided 95% CI was above -10%.

The clinically evaluable (CE) population included all participants in the mITT population who met the criteria for study inclusion, received the full-course of study

treatment, and underwent an assessment for clinical cure at the PTE. Non-inferiority was concluded if the lower bound of the 2-sided 95% CI was above -10%.

The microbiologically evaluable (ME) population was the mITT population in whom a gram-positive pathogen known to cause ABSSSI was detected at baseline and who could be evaluated clinically.

The safety population included all randomised participants who receive a dose of either oritavancin or vancomycin.

Results table for Corey et al. 2015

Outcome	Oritivancin IV	Vancomycin IV	Analysis
Primary outcome	**n=503**	**n=502**	**-**
Early clinical response at ECE (mITT population)	403/503 (80.1%)	46/502 (82.9%)	Treatment difference -2.7% (95% CI -7.5% to 2.0% [non-inferiority margin met])
Secondary outcomes	**n=503**	**n=502**	**-**
Investigator-assessed clinical cure at PTE (mITT population)	416/503 (82.7%)	404/502 (80.5%)	Treatment difference 2.2% (95% CI -2.6% to 7.0% [non-inferiority margin met])
Lesion size reduction of 20% or more at ECE (mITT population)	432/503 (85.9%)	428/502 (85.3%)	Treatment difference 0.6% (95% CI -3.7% to 5.0% [non-inferiority margin met])
Early clinical response at ECE (CE population)	357/427 (83.6%)	358/408 (87.7%)	Treatment difference -4.1% (95% CI -8.9% to 6.0% [non-inferiority margin met])
Investigator-assessed clinical cure at PTE (CE population)	398/427 (93.2%)	387/408 (94.9%)	Treatment difference -1.6% (95% CI -4.9% to 1.6% [non-inferiority margin met])
Lesion size reduction of 20% or more at ECE (CE population)	378/427 (88.5%)	364/408 (89.2%)	Treatment difference -0.7% (95% CI -5.0% to 3.6% [non-

			inferiority margin met])
Early clinical response at ECE (people with MRSA in the MicroITT population)	82/100 (82.0%)	82/101 (81.2%)	Treatment difference 0.8% (95% CI -9.9% to 11.5%)
Investigator-assessed clinical cure at PTE (people with MRSA in the MicroITT population)	84/100 (84.0%)	86/101 (85.1%)	Treatment difference -1.1% (95% CI -11.1% to 8.8%)
Lesion size reduction of 20% or more at ECE(people with MRSA in the MicroITT population)	96/100 (96.0%)	91/101 (90.1%)	Treatment difference 5.9% (95% CI -1.1% to 12.9%)
Early clinical response at ECE (people with MSSA in the MicroITT population)	126/150 (84.0%)	137/157 (87.3%)	Treatment difference -3.3% (95% CI -11.1 to 4.6)
Investigator-assessed clinical cure at PTE (people with MSSA in the MicroITT population)	130/150 (86.7%)	136/157 (86.6%)	Treatment difference 0% (95% CI -7.6% to 7.7%)
Lesion size reduction of 20% or more at ECE (people with MSSA in the MicroITT population)	131/150 (87.3%)	135/157 (86.0%)	Treatment difference 1.3% (95% CI -6.3% to 8.9%)
Safety outcomes	**n=503**	**n=502**	**-**
At least 1 treatment-emergent adverse event	256/503 (50.9%)	252/502 (50.2%)	No statistical analysis reported
Serious adverse events	22/503 (4.4%)	23/502 (4.6%)	No statistical analysis reported
Deaths	1/503 (0.2%)	1/502 (0.2%)	No statistical analysis reported
Treatment-related adverse events	109/503 (21.7%)	128/502 (25.5%)	No statistical analysis reported
Treatment-emergent adverse events resulting in treatment discontinuation	18/503 (3.6%)	13/502 (2.6%)	No statistical analysis reported
Nausea	45/503 (8.9%)	60/502 (12.0%)	No statistical analysis reported
Headache	35/503 (7.0%)	28/502 (5.6%)	No statistical analysis reported
Vomiting	22/503 (4.4%)	28/502 (5.6%)	No statistical analysis reported
Abscess on limb	14/503 (2.8%)	8/502 (1.6%)	No statistical analysis reported
Osteomyelitis	5/503 (1.0%)	0/502 (0.0%)	Reported from the EPAR

Abbreviations: IV, intravenous; CI, confidence interval; mITT, modified intent-to-treat; CE, clinically evaluable; ECE, early clinical evaluation; MicroITT, microbiological

intent-to-treat; MRSA, meticillin-resistant *Staphylococcus aureus*; MSSA, meticillin-susceptible *Staphylococcus aureus*; and PTE, post-therapy evaluation

The modified intent-to-treat (mITT) population included all randomised participants who received either oritavancin or vancomycin. Non-inferiority was concluded if the lower bound of the 2-sided 95% CI was above -10%.

The clinically evaluable (CE) population included all participants in the mITT population who met the criteria for study inclusion, received the full-course of study treatment, and underwent an assessment for clinical cure at the PTE. Non-inferiority was concluded if the lower bound of the 2-sided 95% CI was above -10%.

The microbiological intent-to-treat (MicroITT) population was the mITT population in whom a gram-positive pathogen known to cause ABSSSI was detected at baseline.

The safety population included all randomised participants who receive a dose of either oritavancin or vancomycin.

Appendix E: Literature search strategy

Database search strategies

Database: Medline
Platform: Ovid
Version: Ovid MEDLINE(R) <1946 to October 05, 2021
Search date: 6/10/21
Number of results retrieved: 110
Search strategy:
ES - ABSSSI - Oritavancin - Medline
---
1 exp Skin Diseases, Infectious/ (121696)
2 exp Skin/ (234255)
3 (skin or ABSSSI).tw. (498761)
4 or/1-3 (692610)
5 (Oritavancin or Orbactiv or KIMYRSA or LY-333328 or LY333328 or Nuvocid or Ramvocid or Tenkasi).af. (378)
6 4 and 5 (122)
7 limit 6 to english language (121)
8 limit 7 to (letter or historical article or comment or editorial or news or case reports) (10)
9 7 not 8 (111)
10 Animals/ not (Animals/ and Humans/) (4861066)
11 9 not 10 (110)
12 remove duplicates from 11 (110)

Database: Medline in-process
Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & In-Data-Review Citations <1946 to October 05, 2021
Search date: 06/10/21
Number of results retrieved: 1
Search Strategy:
---
1 exp Skin Diseases, Infectious/ (0)
2 exp Skin/ (0)
3 (skin or ABSSSI).tw. (7123)
4 or/1-3 (7123)
5 (Oritavancin or Orbactiv or KIMYRSA or LY-333328 or LY333328 or Nuvocid or Ramvocid or Tenkasi).af. (4)
6 4 and 5 (1)
7 limit 6 to english language (1)
8 limit 7 to (letter or historical article or comment or editorial or news or case reports) (0)
9 7 not 8 (1)
10 Animals/ not (Animals/ and Humans/) (0)
11 9 not 10 (1)
12 remove duplicates from 11 (1)

Database: Medline epubs ahead of print
Platform: Ovid
Version: Epub Ahead of Print <October 05, 2021
Search date: 6/10/21
Number of results retrieved: 2
Search strategy:
1 exp Skin Diseases, Infectious/ (0)
2 exp Skin/ (0)
3 (skin or ABSSSI).tw. (7552)
4 or/1-3 (7552)
5 (Oritavancin or Orbactiv or KIMYRSA or LY-333328 or LY333328 or Nuvocid or Ramvocid or Tenkasi).af. (8)
6 4 and 5 (2)
7 limit 6 to english language (2)
8 limit 7 to (letter or historical article or comment or editorial or news or case reports) (0)
9 7 not 8 (2)
10 Animals/ not (Animals/ and Humans/) (0)
11 9 not 10 (2)
12 remove duplicates from 11 (2)

Database: Medline daily update
Platform: Ovid
Version: MEDLINE(R) Daily Update <October 05, 2021
Search date: 6/10/21
Number of results retrieved:
Search strategy
1 exp Skin Diseases, Infectious/ (144)
2 exp Skin/ (339)
3 (skin or ABSSSI).tw. (940)
4 or/1-3 (1149)
5 (Oritavancin or Orbactiv or KIMYRSA or LY-333328 or LY333328 or Nuvocid or Ramvocid or Tenkasi).af. (1)
6 4 and 5 (1)
7 limit 6 to english language (1)
8 limit 7 to (letter or historical article or comment or editorial or news or case reports) (0)
9 7 not 8 (1)
10 Animals/ not (Animals/ and Humans/) (4744)
11 9 not 10 (1)
12 remove duplicates from 11 (1)

Database: Embase
Platform: Ovid
Version: Embase <1974 to 2021 October 05
Search date: 6/10/21
Number of results retrieved: 376
Search strategy:
1 exp Skin Diseases, Infectious/ (174176)

2 exp Skin/ (387145)
3 (skin or ABSSSI).tw. (759185)
4 or/1-3 (1048225)
5 (Oritavancin or Orbactiv or KIMYRSA or LY-333328 or LY333328 or Nuvocid or Ramvocid or Tenkasi).af. (1273)
6 4 and 5 (475)
7 limit 6 to english language (469)
8 7 not (letter or editorial).pt. (453)
9 nonhuman/ not (human/ and nonhuman/) (4866854)
10 8 not 9 (434)
11 (conference abstract or conference paper or conference proceeding or "conference review").pt. (4980610)
12 10 not 11 (371)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL
ES - ABSSSI - Oritavancin - Cochrane

Platform: Wiley
Version:
CDSR –Issue 10 of 12, October 2021
CENTRAL – Issue 10 of 12, October 2021
Search date: 8/10/21
Number of results retrieved: CDSR 0; CENTRAL 29
Search strategy:
Search Name: ES - ABSSSI - Oritavancin - Cochrane

Date Run: 08/10/2021 12:15:41
Comment:

ID	Search	Hits
#1	MeSH descriptor: [Skin Diseases, Infectious] explode all trees	3475
#2	MeSH descriptor: [Skin] explode all trees	4607
#3	(skin or ABSSSI):ti,ab,kw	61150
#4	#1 or #2 or #3	63547
#5	(Oritavancin or Orbactiv or KIMYRSA or LY-333328 or LY333328 or Nuvocid or Ramvocid or Tenkasi):ti,ab,kw	35
#6	#4 and #5	29

Database: EUnetHTA (Oritavancin, no results 8/10/21)
(Oritavancin OR Orbactiv OR KIMYRSA OR LY-333328 OR LY333328 OR Nuvocid): domain www.eunethta.eu/assessments/ (no results 8/10/21)

Database: INAHTA database
Search date: 5/10/21
Number of results retrieved: 0
Search strategy: (Oritavancin OR Orbactiv OR KIMYRSA OR LY-333328 OR Nuvocid OR Ramvocid OR Tenkasi)

Appendix F: Excluded studies

Study reference	Reason for exclusion
Zhang, Huan et al. (2021) Efficacy and safety of oritavancin for the treatment of acute bacterial skin and skin-structure infections: a systematic review and meta-analysis. Journal of global antimicrobial resistance; vol. 25; 380-389	Not best available evidence (population in 2 included studies do not meet the PICO).
Corey, G Ralph et al. (2018) Single intravenous dose of oritavancin for treatment of acute skin and skin structure infections caused by gram-positive bacteria: summary of safety analysis from the phase 3 SOLO studies. Antimicrobial agents and chemotherapy; vol. 62 (no. 4)	Not best available evidence (duplicated population from main studies).
Lodise, Thomas et al. (2017) Efficacy and safety of oritavancin relative to vancomycin for patients with acute bacterial skin and skin structure infections (ABSSSIs) in the outpatient setting: Results from the solo clinical trials. Open Forum Infectious Diseases; vol. 4 (no. 1); 1-9	Not best available evidence (duplicated population from main studies).
Corey, G Ralph et al. (2016) Pooled analysis of single-dose oritavancin in the treatment of acute bacterial skin and skin-structure infections caused by gram-positive pathogens, including a large patient subset with methicillin-resistant *Staphylococcus aureus*. International journal of antimicrobial agents; vol. 48 (no. 5); 528-534	Not best available evidence (duplicated population from main studies).
Deck, Daniel H et al. (2016) Single-dose oritavancin treatment of acute bacterial skin and skin structure infections: SOLO trial efficacy by eron severity and management setting. Infectious Diseases and Therapy; vol. 5 (no. 3); 353-361	Not best available evidence (duplicated population from main studies).
Rubino, C M et al. (2015). Population pharmacokinetic analysis for a single 1,200-milligram dose of oritavancin using data from two pivotal phase 3 clinical trials. Antimicrobial agents and chemotherapy; vol. 59 (no. 6); 3365-72	Not best available evidence (outcomes do not meet the PICO).
Redell, Mark et al (2018). A real-world patient registry for oritavancin demonstrates efficacy and safety consistent with the phase 3 SOLO program. Open Forum Infectious Diseases; vol. 5 (no. 6); ofy051	Not best available evidence (No comparator).
Williams, Brandy et al. (2021) Comparison of Inpatient Standard-of-Care to Outpatient Oritavancin Therapy for Patients With Acute Uncomplicated Cellulitis. Journal of Pharmacy Practice	Not best available evidence (outcomes do not meet the PICO).
Ahiskali, Aileen; Rhodes, Heather (2020) Oritavancin for the treatment of complicated gram-positive infection in persons who inject drugs. BMC Pharmacology and Toxicology; vol. 21 (no. 1); 73	Not best available evidence (No comparator).