NICE National Institute for Health and Care Excellence

NICE advice

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

Evidence summary
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Product overview

The content of this evidence summary 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.

Oritavancin (Tenkasi, Menarini) is a glycopeptide antibiotic given intravenously as a single dose. It has a marketing authorisation for treating acute bacterial skin and skin structure infections (ABSSSI) in adults.

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. Follow recommendations on new antimicrobials in the NICE guideline on antimicrobial stewardship.

Rationale

ABSSSI are common bacterial infections that may require systemic antibiotics, surgical management, and hospitalisation. The most common bacteria associated with ABSSSI is *Staphylococcus aureus* (*S.aureus*). Resistance has been reported in *S. aureus*, such as meticillin-resistant *S. aureus* (MRSA), where choice of treatment can be challenging (European public assessment report [EPAR] on oritavancin).

Evidence from 2 phase-3, randomised controlled trials in non-UK hospitals (n=968 and n=1,019) found oritavancin was non-inferior to vancomycin for treating ABSSSI caused by gram-positive pathogens in adults. Oritavancin was administered as a single 3-hour infusion and vancomycin was administered twice daily over 7 to 10 days.

The infections treated in the studies were cellulitis or erysipelas, abscesses, and wound infections. The median lesion area was between 225 cm^2 and 309 cm^2 and people had at least 2 signs of systemic infection, indicating that the infections were severe.

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 (summary of product characteristics [SPC] for oritavancin).

The NICE guideline on antimicrobial stewardship makes recommendations on the effective use of new antimicrobials. Oritavancin should be reserved for those people most likely to benefit from it, after specialist microbiological advice to help monitor use and limit

antimicrobial resistance.

Factors for decision making

Effectiveness and safety

Evidence was from 2 phase-3, multicentre, 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 a single dose of intravenous oritavancin with twice daily intravenous vancomycin to treat ABSSSI in adults with cellulitis or erysipelas, wound infection or major cutaneous abscess. Aztreonam or metronidazole was allowed for people with mixed infections (where gram-negative or anaerobic bacteria were suspected respectively) in both arms of both studies.

The 2 studies found that oritavancin was non-inferior to vancomycin for the primary end point, early clinical response after 48 to 72 hours of administration. 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. 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. 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.

Oritavancin was non-inferior to vancomycin for the key secondary end point of investigator-assessed clinical cure 7 to 14 days after treatment finished. This end point was the primary end point for the European Medicines Agency submission (EPAR on oritavancin). Success was defined as complete resolution of signs and symptoms. 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. 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. Oritavancin was also found to be non-inferior to vancomycin for the secondary endpoint of a 20% or more reduction in lesion size in both studies.

The most common pathogen detected at baseline was *S. aureus*, including MRSA. Within the population evaluated microbiologically, Corey et al. 2014 found that 46.6% of people had MRSA and Corey et al. 2015 found that 38.4% of people had MRSA. For this subpopulation of people with MRSA at baseline, approximately 80% of people in both

treatment arms in both studies met the definition of success for early clinical response after 48 to 72 hours of administration.

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.

The SPC for oritavancin states that the most commonly reported adverse reactions were nausea, hypersensitivity reactions, infusion site reactions and headache. The most common 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. Suspected adverse reactions associated with oritavancin should be reported via the Yellow Card Scheme.

Limitations of the evidence

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.

In both studies, vancomycin was used as the comparator, and each study site could choose to administer a dose of either 1 g or 15 mg/kg every 12 hours. The lack of standardised dosing in the vancomycin arm may have impacted the results, although the cure rates with vancomycin were within the expected range (EPAR on oritavancin). The

NICE antimicrobial prescribing guideline on cellulitis and erysipelas recommends vancomycin as an option only when MRSA is suspected or confirmed. 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. 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.

Person-centred factors

Oritavancin is given intravenously as a single infusion over 3 hours. It has a prolonged half-life (approximately 245 hours) allowing for a single dose treatment course. It is likely to be prescribed in a hospital setting. Specialists who commented on this evidence review highlighted that in practice oritavancin is likely to be provided in an ambulatory care setting or through OPAT for people with severe 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.

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

Antimicrobial resistance

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

resistance can be found on UK Health Security Agency antimicrobial resistance local indicators.

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.

See the full evidence review for more information.

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