



# Antimicrobial prescribing: delafloxacin for acute bacterial skin and skin structure infections

Evidence summary

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[www.nice.org.uk/guidance/es32](http://www.nice.org.uk/guidance/es32)

## Product overview

The content of this evidence summary was up to date in December 2020. See [summaries of product characteristics](#), [British National Formulary \(BNF\)](#) or the [Medicines and Healthcare products Regulatory Agency \(MHRA\)](#) or the [NICE](#) websites for up-to-date information.

Delafloxacin (Quofenix, Menarini) is a fluoroquinolone antibiotic, which is available as a powder for infusion and a tablet. It has a marketing authorisation for treating acute bacterial skin and skin structure infections (ABSSSI) in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections.

# Advisory statement on likely place in therapy

Delafloxacin may be an option for adults needing hospital treatment for severe acute bacterial skin and skin structure infections (ABSSSI), primarily cellulitis or erysipelas, abscesses and wound infections, when standard oral and intravenous treatments are not suitable. Evidence supports the use of intravenous delafloxacin in these circumstances, with a switch to oral treatment after 3 days if possible. Take account of local antimicrobial resistance and seek specialist microbiological advice. Follow the recommendations on new antimicrobials in the [NICE guideline on antimicrobial stewardship](#).

## Rationale

The [European Public Assessment Report \(EPAR\) for delafloxacin](#) states that most ABSSSI remain susceptible to penicillin and beta-lactam antibiotics, but antibiotic resistance is becoming more common. ABSSSI can be caused by several pathogens, with gram-negative and anaerobic pathogens found alongside gram-positive organisms, particularly in people with comorbidities and those previously treated with antibiotics.

Two phase 3 randomised controlled trials in over 1,500 adults with ABSSSI attending non-UK hospitals found that delafloxacin was non-inferior to vancomycin plus aztreonam for reducing lesion size (erythema) by at least 20% after 48 hours to 72 hours, and resolving signs and symptoms at 14 days.

One of the studies investigated intravenous delafloxacin only and the other investigated intravenous delafloxacin for 3 days followed by oral delafloxacin. There is no direct evidence to support using the oral formulation alone. Delafloxacin has not been compared with other treatments in phase 3 studies.

The infections treated in the studies were cellulitis or erysipelas, abscesses and wound infections. The mean erythema size of the lesion was around 300 cm<sup>2</sup> or more in both studies and participants had at least 2 signs of systemic infection, showing that the infections were severe.

Delafloxacin offers the potential for treating infections caused by gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), and gram-negative pathogens, without the need for combination therapy. It appears to be well-

tolerated, but its full adverse effect profile is not yet known. In the [MHRA drug safety update in March 2019](#), the MHRA issued new restrictions and precautions for fluoroquinolone antibiotics because of very rare reports of disabling and potentially long-lasting or irreversible adverse effects affecting musculoskeletal and nervous systems. The EPAR states that the possibility of class effects of fluoroquinolones (such as tendon rupture) with delafloxacin cannot be excluded, although some data suggest a possible safety benefit of delafloxacin compared to other fluoroquinolones, in particular for QT prolongation and phototoxicity. Suspected adverse reactions associated with delafloxacin should be reported via the [Yellow Card Scheme](#).

The [NICE guideline on antimicrobial stewardship](#) makes recommendations on the effective use of new antimicrobials. Delafloxacin 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 multicentre, randomised, double-blinded phase 3 studies, which compared delafloxacin monotherapy with vancomycin plus aztreonam for treating for acute bacterial skin and skin structure infections (ABSSSI) in adults with cellulitis or erysipelas, wound infection, major cutaneous abscess or burn infection (minimum surface area 75 cm<sup>2</sup>) and at least 2 signs of systemic infection. [Pullman et al. \(2017\)](#) investigated intravenous delafloxacin only (n=660), whereas [O'Riordan et al. \(2018\)](#) investigated intravenous delafloxacin for 3 days followed by oral delafloxacin (n=850). Duration of treatment in both studies ranged from 5 days to 14 days. Aztreonam was added to vancomycin to treat gram-negative ABSSSI and was stopped if baseline cultures were confirmed negative for gram-negative pathogens. In both studies, people could receive treatment as a hospital inpatient or outpatient.

The 2 studies found that delafloxacin was non-inferior to vancomycin plus aztreonam for reducing lesion size (erythema) by at least 20% after 48 hours to 72 hours. Overall, this improvement was seen in around 80% of people in both treatment groups in both studies. Delafloxacin was also non-inferior to vancomycin plus aztreonam for investigator-assessed clinical cure (complete resolution of signs and symptoms) at 14 days in both studies. Overall, clinical cure was seen in over half of people at day 14 and over two-thirds of

people at day 21 to day 28 across the arms of the 2 studies.

The most common pathogen in both studies was *Staphylococcus aureus* (including MRSA), which was found in around 60% of people with pathogens identified at baseline. At day 14, rates of documented or presumed eradication of this pathogen were 98.5% with delafloxacin and 96.6% with vancomycin plus aztreonam in O'Riordan et al. (2018), and 98.3% with both treatments in Pullman et al. (2017). Rates of successful treatment of MRSA infections were similar.

Treatment-related adverse events were seen in 20.9% of people in both treatment groups in O'Riordan et al. (2018), and 24.1% of people in the delafloxacin group and 32.8% of people in the vancomycin and aztreonam group in Pullman et al. (2017). Fewer people taking delafloxacin stopped treatment because of treatment-related adverse events compared with vancomycin plus aztreonam (1.2% compared with 2.4% respectively in O'Riordan et al. 2018 and 0.3% compared with 2.5% respectively in Pullman et al. 2017). No statistical analyses were reported for safety data.

The [summary of product characteristics for delafloxacin](#) states that the most common adverse drug reactions reported with delafloxacin in phase 2 and 3 studies in ABSSSI were diarrhoea and nausea (6.9% and 7.8%, respectively), which were mild to moderate in intensity. Other common adverse reactions (in between 1 in 10 people and 1 in 100 people) were fungal infection, headache, vomiting, hypertransaminasaemia (raised liver transaminases), pruritus and infusion site reactions.

Regarding *Clostridioides difficile* (*C. difficile*) diarrhoea, the [European Public Assessment Report \(EPAR\) for delafloxacin](#) notes that no relevant signal could be identified for delafloxacin based on pooled and individual study data. Across the studies, 1 person had *C. difficile* infection but was previously treated with co-trimoxazole and clindamycin (O'Riordan et al. 2018).

In March 2019, the MHRA recommended prescribing restrictions and precautions for fluoroquinolone antibiotics because disabling, long-lasting or potentially irreversible adverse reactions affecting musculoskeletal and nervous systems have been reported very rarely. Warnings include stopping treatment at first signs of a serious adverse reaction (such as tendonitis), prescribing with special caution for people over 60 years and avoiding coadministration with a corticosteroid ([MHRA drug safety update](#)). In September 2020, the [European Pharmacovigilance Risk Assessment Committee](#), which is the European Medicines Agency (EMA) committee responsible for assessing and monitoring

the safety of human medicines, reported that fluoroquinolones are associated with heart valve regurgitation or incompetence, cervical artery dissection, and aortic aneurysm and dissection ([EMA/PRAC/458924/2020](#)). The possibility of class effects of fluoroquinolones cannot yet be excluded for delafloxacin (EPAR).

## Limitations of the evidence

The participants included in the studies were mostly under 65 and of white ethnicity, and the incidence of diabetes was lower than in the general population. Therefore, the study populations may not be representative of people who are most likely to have a severe skin infection, such as older adults and people with diabetes (who often have impaired vascular perfusion).

Most of the people in the studies had severe cellulitis or erysipelas, abscesses and wound infections. Few participants had burn infections or surgical site infections. People with human and animal bites, diabetic foot infection, osteomyelitis, decubitus ulcer and certain other infections were excluded from the studies. Only around a fifth of participants had previously used another antibiotic (type not reported).

Delafloxacin has been compared only with vancomycin and aztreonam, which is not a standard treatment option in the UK. The [NICE antimicrobial prescribing guideline on cellulitis and erysipelas](#) recommends vancomycin as an option only when MRSA is suspected or confirmed. Aztreonam is not a treatment option in the guideline. The EPAR considered vancomycin to be an acceptable comparator for delafloxacin because of the proportion of MRSA pathogens identified in the studies (21.0% and 34.5%). Aztreonam was added for treating gram-negative ABSSSI and was stopped if baseline cultures were confirmed negative for gram-negative pathogens.

The EPAR states that, although delafloxacin potentially has a better safety profile than other fluoroquinolones because of its different chemical structure, this has not yet been proven.

## Person-centred factors

Delafloxacin infusion is administered intravenously every 12 hours, over 1 hour. As in the studies, it is likely to be used in a hospital setting for people with severe infections. Specialists advised that it is likely to be considered when other antibiotics cannot be used;

for example, in people with multiple allergies and intolerances (including severe penicillin allergy) and renal failure, people taking other medicines that interact with the standard antibiotic options, or in people who develop myelosuppression with linezolid. It does not need weight-based dosing or drug monitoring, which may mean fewer blood tests for people with ABSSSI than with some other intravenous treatments.

There is no direct evidence to support using oral delafloxacin alone for ABSSSI, but delafloxacin infusion may be switched to delafloxacin tablets at the prescriber's discretion. The 300-mg infusion and 450-mg tablet formulations are bioequivalent. People are likely to prefer switching to oral treatment because of the ability to return home, ease of administration and convenience compared with ongoing intravenous treatment.

[Public Health England's start smart – then focus guidance](#) and the [NICE guideline on antimicrobial stewardship](#) recommend that intravenous antibiotic prescriptions should be reviewed at 48 hours to 72 hours, documenting response to treatment and any available microbiology results to determine if the antibiotic should be continued or switched to a narrower spectrum or an oral antibiotic.

## Antimicrobial resistance

Delafloxacin is a new antimicrobial, so data on resistance and the impact on clinical practice in the UK are limited. Information on resistance can be found in [Public Health England's antimicrobial resistance local indicators](#).

The EPAR notes that development of resistance to delafloxacin is a concern and should be closely monitored when delafloxacin is used in clinical practice.

## Resource implications

The cost of delafloxacin 300-mg powder for concentrate for solution for infusion is £61.50 for 1 vial. The cost of 1 delafloxacin 450-mg oral tablet is also £61.50 ([BNF information on delafloxacin](#)). This cost is for the medicine only and does not include any associated costs related to antibiotic administration in hospital.

Delafloxacin is given every 12 hours and the recommended total duration of treatment is 5 days to 14 days. The recommended treatment duration in the NICE antimicrobial prescribing guideline on cellulitis and erysipelas is 7 days for severe infection, which would

cost £861.

See the [full evidence review](#) for more information.

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