NICE National Institute for Health and Care Excellence

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

Evidence review

Publication date January 2021

This evidence review sets out the best available evidence on delafloxacin for treating acute bacterial skin and skin structure infections (ABSSSI) in adults when it is considered inappropriate to use other antibiotics that are commonly recommended for the initial treatment of these infections. The evidence review 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 December 2020. 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.

ISBN: 978-1-4731-3950-3

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Background

Acute bacterial skin and skin structure infections (ABSSSI) are common bacterial infections, which include cellulitis, erysipelas, wound infections (traumatic or post-surgical) and major abscesses. Cellulitis and skin abscesses are commonly encountered in the community setting and frequently result in hospitalisation. ABSSSI are also seen in the hospital setting; for example, surgical site infections (European public assessment report [EPAR] on delafloxacin).

In 2017 to 2018 there were over 88,000 recorded admissions to hospital in England for cellulitis, with more than 80,000 of these being emergency admissions, and accounting for over 430,000 bed days. Also, there were over 42,000 admissions (including more than 36,000 emergency admissions) for skin abscesses, boils and carbuncles, accounting for over 85,000 bed days (NHS Digital's hospital admitted patient care activity, 2017-18).

Management of ABSSSI depends on the clinical presentation and the severity of the infection. Antibiotic treatment should be offered. 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 methicillin-resistant *Staphylococcus aureus* (MRSA) status should be taken into account when choosing an antibiotic. There are also published NICE antimicrobial prescribing guidelines on human and animal bites and insect bites and stings, and a NICE antimicrobial prescribing guideline on skin abscesses is being developed.

The most common bacteria identified in ABSSSI are gram-positive pathogens, including streptococci and staphylococci, and most ABSSSI remain susceptible to penicillin and beta-lactam antibiotics (EPAR information on delafloxacin).

Antibiotic resistance is becoming more common in ABSSSI. The English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) report for 2019 to 2020 states that there was a 32% increase in the estimated number of antibiotic-resistant bloodstream infections caused by key bacterial species (including *Staphylococcus aureus* [*S. aureus*]) between 2015 and 2019. Resistance to *S. aureus* gradually declined in 2019 and only 6% of bloodstream isolates were methicillin-resistant. However, the burden of infection increased because the

incidence of *S. aureus* increased by 14% between 2015 and 2019. The ESPAUR report does not include data specifically for ABSSSI.

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. Gram-negative pathogens are common in some types of surgical site infection. Many established and recently approved antibiotics for ABSSSI provide only gram-positive coverage. However, many options are available to provide gram-negative coverage (for example, cephalosporins, carbapenems, ureido-penicillins, aminoglycosides or quinolones) (EPAR).

The EPAR notes that, although fluoroquinolones (such as levofloxacin, ofloxacin and moxifloxacin) may be indicated for ABSSSI, they have limitations and carry a risk of severe adverse effects. In an MHRA drug safety update on fluoroquinolone antibiotics 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.

This evidence review considers the evidence for the safety and efficacy of a new fluoroquinolone antibiotic, delafloxacin.

Product overview

Mode of action

Delafloxacin is a fluoroquinolone antibiotic. It inhibits bacterial enzymes (topoisomerase 4 and DNA gyrase [topoisomerase 2]) that are needed for bacterial DNA replication, transcription, repair and recombination (summary of product characteristics (SPC) for delafloxacin). Delafloxacin has a different chemical structure from other fluoroquinolones, which enables it to enter bacterial cells more easily (EPAR information on delafloxacin).

Clinical efficacy of delafloxacin has been shown for a range of gram-positive and gram-negative pathogens commonly seen in acute bacterial skin and skin structure infections (ABSSSI), including MRSA (SPC).

Regulatory status

Delafloxacin has a marketing authorisation for treating ABSSSI in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections (SPC).

Dosing information

Delafloxacin is available as a 300-mg powder for concentrate for solution for infusion and as a 450-mg oral tablet. The 300-mg infusion and 450-mg tablet formulations are bioequivalent.

The recommended dosage of delafloxacin infusion is 300 mg intravenously every 12 hours, administered over 1 hour. The SPC states that treatment may be switched to delafloxacin tablets at the prescriber's discretion. The recommended dosage of delafloxacin tablets is 450 mg every 12 hours. The recommended total duration of treatment with delafloxacin is 5 to 14 days (SPC).

See the person-centred factors section of this evidence review for more information on using delafloxacin and, in particular, switching between intravenous and oral treatment.

Antimicrobial resistance

Resistance to fluoroquinolones, including delafloxacin, can occur because of mutations in defined regions of the target bacterial enzymes topoisomerase 4 and DNA gyrase, referred to as quinolone-resistance determining regions, or through other resistance mechanisms such as efflux mechanisms. There may be cross-resistance between delafloxacin and other fluoroquinolones, although some isolates resistant to other fluoroquinolone may retain susceptibility to delafloxacin (SPC).

The English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report 2019 to 2020 states that the number of gram-negative bloodstream infections that are resistant to fluoroquinolones has increased, which may be driven by increased use in secondary care. According to the report, use of levofloxacin almost doubled in secondary care between 2015 and 2019.

Objective

This evidence review considers the best available evidence on the effectiveness and safety of delafloxacin 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.

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 clinical effectiveness of delafloxacin for treating ABSSSI in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections?

2. What is the safety of delafloxacin for treating ABSSSI in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections?

3. From the evidence selected, are there any subgroups of people who may benefit from delafloxacin more than the wider population of interest?

Summary of included studies

A literature search for delafloxacin for treating ABSSSI identified 15 references (see appendix E for full details). These references were screened using their titles and abstracts and 9 full text references were obtained and assessed for relevance.

Two studies are included in this evidence summary. They are multicentre, randomised, double-blinded phase 3 studies, which compared delafloxacin monotherapy with vancomycin plus aztreonam for treating ABSSSI in adults with cellulitis or erysipelas, wound infection, major cutaneous abscess or burn infection (minimum surface area 75 cm^2) 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 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.

A summary of the included studies is shown in appendix B. Quality assessment of the included studies is in appendix C.

Seven 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 clinical effectiveness of delafloxacin for treating acute bacterial skin and skin structure infections in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections?

Clinical response

Both studies found that delafloxacin monotherapy was similar to vancomycin plus aztreonam for reducing lesion size (erythema) by at least 20% after 48 hours to 72 hours in adults with cellulitis or erysipelas, wound infection, major cutaneous abscess or burn infection and at least 2 signs of systemic infection (US Food and Drug Administration primary outcome). Overall, this clinical response was seen in around 80% of people in both treatment groups in both studies.

In O'Riordan et al. (2018), lesion size was reduced in 83.7% of people given delafloxacin (intravenous then oral) and 80.6% of people given vancomycin plus aztreonam (difference 3.1%, 95% CI -2.0 to 8.3 [non-inferior]). In Pullman et al. (2017), lesion size was reduced in 78.2% of people given delafloxacin (intravenous only) and 80.9% of people given vancomycin plus aztreonam (difference -2.6%, 95% CI -8.8 to 3.6 [non-inferior]).

Clinical success

Delafloxacin and vancomycin plus aztreonam were similar in terms of investigator-assessed clinical cure (complete resolution of signs and symptoms) at 14 days in

adults with acute bacterial skin and skin structure infections (ABSSSI) in both studies (European Medicines Agency primary outcome). 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.

O'Riordan et al. (2018) found that signs and symptoms resolved in 57.7% of people in the delafloxacin group and 59.7% of people in the vancomycin plus aztreonam group (difference -2.0%, 95% CI -8.6 to 4.6 [non-inferior]). Pullman et al. (2017) found that signs and symptoms resolved in 52.0% of people in the delafloxacin group and 50.5% of people in the vancomycin plus aztreonam group (difference 1.5%, 95% CI -6.1 to 9.1 [non-inferior]).

The proportions of people considered cured increased by day 21 to day 28 in both studies, with no differences between the treatment groups. At this time, lesions resolved in 67.8% of people in the delafloxacin group and 71.0% of people in the vancomycin plus aztreonam group (difference -3.1%, 95% CI -9.3 to 3.1 [non-inferior]) in O'Riordan et al. (2018). Similarly, lesions resolved in 70.4% of people in the delafloxacin group and 66.6% of people in the vancomycin plus aztreonam group (difference 3.8%, 95% CI -3.3 to 10.9 [non-inferior]) in Pullman et al. (2017).

Microbiological response

The most common pathogen in both studies was *S. 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. No statistical analyses were presented for microbiological response.

Microbiological response rates were also high and comparable between the treatment groups for other pathogens that cause ABSSSIs, including gram-negative bacteria.

Review question 2: What is the safety of delafloxacin for treating ABSSSI in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections?

Treatment-emergent adverse events were seen in 43.6% of people given delafloxacin and 39.3% of people given vancomycin and aztreonam in O'Riordan et al. (2018), and 47.5% of people given delafloxacin and 59.2% of people given vancomycin and aztreonam in Pullman et al. (2017). No statistical analyses were presented for safety data.

Serious adverse events occurred in about 4% of people in both groups in both studies. Two people from the vancomycin plus aztreonam group died in the study by O'Riordan et al. (2018) and 1 person in each treatment group died in the study by Pullman et al. (2017). No deaths were considered related to study treatment.

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 than 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.

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.

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 older than 60 and avoiding coadministration with a corticosteroid (MHRA drug safety update for fluoroquinolone antibiotics).

In September 2020, the Pharmacovigilance Risk Assessment Committee (PRAC), which is the European Medicines Agency (EMA) committee responsible for assessing and monitoring the safety of human medicines, reported that fluoroquinolones are associated with development of heart valve regurgitation or incompetence, cervical artery dissection, and aortic aneurysm and dissection. The PRAC recommended that product information for fluoroquinolones is updated with these risks (EMA/PRAC/458924/2020).

The European public assessment report (EPAR) on delafloxacin concludes that, overall, the safety profile of delafloxacin appears to be comparable to that of other fluoroquinolones. It notes that it is not possible to identify rare and very rare events for delafloxacin because of the limited size of the safety database and so the possibility of class effects of fluoroquinolones (such as tendon rupture as detailed above) cannot be excluded. Suspected adverse reactions associated with delafloxacin should be reported via the Yellow Card Scheme.

Regarding *Clostridioides difficile* (*C. difficile*) diarrhoea, the EPAR 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). No safety signal for potential phototoxicity was identified for delafloxacin based on pooled and individual study data, and no clinically significant QT prolongation was apparent (EPAR).

Review question 3: From the evidence selected, are there any subgroups of people who may benefit from delafloxacin more than the wider population of interest?

No subgroups of people were identified from the studies who may benefit from delafloxacin more than the wider population of interest.

Limitations of the evidence

The participants included in the studies were mostly relatively young and of white ethnicity, and Pullman et al. (2017) note that the incidence of diabetes in their study was lower than in the general population. In O'Riordan et al. (2018) and Pullman et

al. (2017) respectively, 81.9% and 93.6% of people were aged 65 or younger; 82.7% and 91.0% of people were white; and 12.6% and 8.6% had diabetes (type not specified). 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).

People with diabetic foot infection, osteomyelitis, decubitus ulcer and certain other infections were excluded from the studies in line with European Medicines Agency (EMA) and US Food and Drug Administration (FDA) guidance on evaluating medicines for ABSSSI. Most participants in the studies had cellulitis or erysipelas, (48.0% and 38.8% respectively), wound infections (26.2% and 35.2% respectively) or major cutaneous abscesses (24.9% and 25.3% respectively, O'Riordan et al. 2018 and Pullman et al. 2017). Fewer than 1% of participants had burn infections in both studies and the number of surgical site infections was also reportedly low. People with human and animal bites were excluded from the studies.

The mean erythema size of the lesion was around 300 cm^2 or more in both studies and participants had at least 2 signs of systemic infection, showing that the infections were severe. In O'Riordan et al. (2018) and Pullman et al. (2017), 23.5% and 18.6% of participants respectively had previously used another antibiotic (type not reported). O'Riordan et al. (2018) investigated intravenous delafloxacin for 3 days followed by oral delafloxacin. There is no direct evidence to support using oral delafloxacin alone.

In ABSSSI, some of the bacteria colonising the lesion and identified in cultures may not be causing the active infection. The methods for identifying the causative organisms in the studies are unclear. Eradication of non-causative bacteria is unlikely to be the cause of resolution of the lesion. It is unclear whether including non-causative bacteria might have affected the results of the studies.

In both studies, vancomycin plus aztreonam was used as the comparator: delafloxacin has not been compared with other antibiotics in phase 3 studies. Aztreonam was added to vancomycin to treat gram-negative ABSSSI and was stopped if baseline cultures were confirmed negative for gram-negative pathogens. The EPAR information on delafloxacin considers that vancomycin may not be the

optimal choice of treatment for some pathogens associated with ABSSSI and linezolid may have been a more appropriate comparator. However, it states that vancomycin is considered acceptable because of the proportion of MRSA pathogens identified (21.0% in O'Riordan et al. 2018 and 34.5% in Pullman et al. 2017). 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.

Non-inferiority of delafloxacin for the primary end point (clinical cure at day 14) was seen in the intention-to-treat (ITT) population (all randomised participants) in O'Riordan et al. (2018), but was not seen in the clinically evaluable population (all randomised participants who completed all activities as defined in the protocol). However, the EPAR states it is acceptable to consider the single primary population ITT for primary analysis and to regard the clinically evaluable population as secondary. Overall, non-inferiority of intravenous as well as intravenous followed by oral delafloxacin is concluded.

The EPAR notes that development of resistance is a concern and should be closely monitored when delafloxacin is used in clinical practice. The EPAR also 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. It reports that some data suggest a possible safety benefit of delafloxacin compared to other fluoroquinolones, in particular for QT prolongation and phototoxicity.

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 for some other intravenous treatments.

The NICE antimicrobial prescribing guidelines on cellulitis and erysipelas and human and animal bites advise that first-line treatment should be oral antibiotics if possible. Also, 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 whether the antibiotic should be continued or switched to a narrower spectrum or an oral antibiotic.

There is no direct evidence to support using oral delafloxacin alone for ABSSSI, but the summary of product characteristics for delafloxacin does state that delafloxacin infusion may be switched to delafloxacin tablets at the prescriber's discretion. The 300-mg infusion and 450-mg tablet formulations are bioequivalent, and evidence from the study by O'Riordan et al. (2018) supports changing intravenous delafloxacin to oral delafloxacin after 3 days. Switching to oral treatment is likely to be preferable to people in terms of ability to return home, ease of administration and convenience compared with ongoing intravenous treatment.

Delafloxacin offers the potential for treating infections caused by gram-positive pathogens (including MRSA) and gram-negative pathogens, without the need for combination therapy. This may mean people will experience fewer interventions with this treatment compared with other antibiotics. It appears to be well-tolerated, although its full adverse effect profile is not yet known.

Resource implications

Both intravenous and oral formulations of delafloxacin are available. The EPAR information on delafloxacin states that availability of both formulations could reduce hospitalisation costs and related risks, and notes that delafloxacin does not need therapeutic drug monitoring.

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 to 14 days. Therefore, the cost of a course of treatment ranges from £615 to £1,722.

The mean duration of treatment was 7 days in O'Riordan et al. (2018) (intravenous delafloxacin for 3 days followed by oral delafloxacin for 4 days) and 6 days in Pullman et al. (2017) (intravenous delafloxacin only). The recommended treatment duration in the NICE antimicrobial prescribing guideline on cellulitis and erysipelas is 7 days for severe infection, which would cost £861.

A wide range of antibiotics, alone or in combination, are used for treating acute bacterial skin and skin structure infections (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, daptomycin or linezolid.

The manufacturer of delafloxacin (Menarini) anticipates that usage will be low, in accordance with good antimicrobial stewardship.

References

O'Riordan W, McManus A, Teras J et al. (2018) A comparison of the efficacy and safety of intravenous followed by oral delafloxacin with vancomycin plus aztreonam for the treatment of acute bacterial skin and skin structure infections: a phase 3, multinational, double-blind, randomized study. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 67(5): 657–666

Pullman J, Gardovskis J, Farley B et al. (2017) Efficacy and safety of delafloxacin compared with vancomycin plus aztreonam for acute bacterial skin and skin structure infections: a phase 3, double-blind, randomized study. The Journal of antimicrobial chemotherapy 72(12): 3471–3480

Development of the evidence review

Process

The NICE 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/organisation	DOI
Dr Philippa Moore, Consultant 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 to ongoing)
Dr Natasha Ratnaraja, Consultant Microbiologist, University Hospitals Coventry & Warwickshire NHS Trust	Microbiologist for BMI Meriden healthcare providing clinical advice (Financial interest October 2018 to ongoing) Council member British Infection Association (Non-financial interest September 2016 to ongoing) Reviewer for NICE (Non-financial interest October 2019 to ongoing)
Dr Tang Shim, Consultant Dermatologist, University Hospitals Coventry & Warwickshire NHS Trust	Paid to attend a British Association of Dermatologist Virtual Meeting, an American Academy Dermatology Virtual Meeting and an Abbvie UK Virtual Advisory Board (financial interests in June and September 2020) Private practice in the BMI Meriden Hospital, and Spire Southbank Hospital (Financial interest July 2019 to ongoing)

Appendices

Appendix A: PICO table

PICO table

Criteria	Details
P – Population and indication	Adults with acute bacterial skin and skin structure infections (when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections)
I – Intervention	Delafloxacin (Quofenix) 450-mg tablets Delafloxacin (Quofenix) 300-mg powder for concentrate for solution for infusion
C – Comparator(s)	Any other plausible strategy or comparator, including: • Placebo or no treatment • Standard current treatment
O – Outcomes	Any outcomes Outcomes may include: • Mortality • Clinical response • Clinical success • Clinical failure • Microbiological response • Adverse effects
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 aged 18 years and over
Date limits	None
Exclusion criteria	-
Publication type	Pre-prints before 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
O'Riordan et al. (2018) Double-blind double-dummy RCT	n=850 (follow up 30 days)	Adults aged 18 years and over (mean age 50.7 years) with ABSSSI (cellulitis or erysipelas, wound infection, major cutaneous abscess or burn infection), at least 75 cm^2 of erythema and at least 2 signs of systemic infection	Delafloxacin 300 mg IV every 12 hours for 3 days then delafloxacin 450 mg orally every 12 hours for a total duration of 5 to14 days Mean total duration 7 days (n=423)	Vancomycin 15 mg/kg IV plus aztreonam 2 g IV every 12 hours for 5 to 14 days. The dose was reduced if renal function was impaired (n=427) Aztreonam or matching placebo treatment was stopped if baseline cultures were confirmed negative for gram-negative pathogens	EMA primary outcome: Investigator-assessed clinical cure at follow up (day 14±1) FDA primary outcome: objective (at least 20% reduction in erythema size in the absence of clinical failure) response 48 hours to 72 hours after starting treatment Secondary outcomes included investigator-assessed success at follow up, investigator-assessed clinical cure at late follow up (day 21 to day 28), microbiological response and adverse events
Pullman et al. (2017) Double-blind RCT	n=660 (follow up 30 days)	Adults aged 18 years and over (mean age 45.8 years) with ABSSSI (cellulitis or erysipelas, wound infection, major cutaneous abscess or burn infection), at least 75 cm^2 of erythema and at least 2 signs of systemic infection	Delafloxacin 300 mg IV every 12 hours for 5 to 14 days Mean total duration 6 days (n=331)	Vancomycin 15 mg/kg IV plus aztreonam 2 g IV every 12 hours for 5 to 14 days (n=329) Aztreonam or matching placebo treatment was stopped if baseline cultures were confirmed negative for gram-negative pathogens	EMA primary outcome: investigator-assessed clinical cure at follow up (day 14±1) FDA primary outcome: objective response (at least 20% reduction in erythema size in the absence of clinical failure) 48 hours to 72 hours after starting treatment Secondary outcomes included investigator-assessed success at follow up, investigator-assessed clinical cure at late follow up (day 21 to day 28), microbiological response and adverse events

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; EMA, European Medicines Agency; FDA, Food and Drug Administration (US); IV, intravenous; RCT, randomised controlled trial.

In both studies, for the EMA primary outcome, investigators' assessment of clinical response was based on ABSSSI signs and symptoms and was categorised as cure (complete resolution); improved (some symptoms but no additional need for antibiotics); failure (additional treatment needed); or indeterminate (incomplete assessment). Investigator-assessed success was defined as cure or improved, with no further antibiotic treatment needed.

For the FDA primary outcome in both studies, clinical failure was defined as less than 20% reduction in erythema; administration of a rescue or non-study antibiotic for the ABSSSI before the primary outcome assessment; unplanned surgical intervention excluding limited bedside debridement and standard wound care before the primary outcome assessment; or death within 72 hours to 74 hours after starting study treatment.

Microbiological response was categorised as documented eradicated (baseline pathogen absent in follow-up cultures); presumed eradicated (no follow-up culture, but clinical success seen); documented persisted (baseline pathogen present in follow-up cultures); or presumed persisted (no follow-up culture, but clinical failure seen).

Appendix C: Quality assessment of included studies

Quality assessment of O'Riordan et al. (2018) and Pullman et al. (2017)

Question	O'Riordan et al. (2018)	Pullman et al. (2017)
Domain 1: Risk of bias arising from the randomisation process	-	-
1.1 Was the allocation sequence random?	Probably yes	Probably yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Probably yes	Probably yes
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No	No
Risk of bias judgement	Low	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	No
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No	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	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	Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	-	-

Question	O'Riordan et al. (2018)	Pullman et al. (2017)
2.1. Were participants aware of their assigned intervention during the trial?	No	No
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No	No
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Not applicable	Not applicable
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	Not applicable	Not applicable
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	Not applicable	Not applicable
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	Low
Domain 3: Missing outcome data	-	-
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes	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	Low
Domain 4: Risk of bias in measurement of the outcome	-	-
4.1 Was the method of measuring the outcome inappropriate?	No	No
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No	No

Question	O'Riordan et al. (2018)	Pullman et al. (2017)
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	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?	Probably yes	Probably 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 (for example scales, definitions, time points) within the outcome domain?	No	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	No
Risk of bias judgement	Low	Low
Overall risk of bias judgement	Low	Low

Abbreviations: Y, yes; PY, probably yes; PN, probably no; N, no; NI, no information.

Checklist used: Cochrane risk of bias 2 tool.

Appendix D: Results tables

Results table for O'Riordan et al. (2018)

Outcome	Delafloxacin (IV then oral)	Vancomycin plus aztreonam	Analysis
Primary outcome	**n=423**	**n=427**	**-**
EMA primary outcome: investigator-assessed clinical cure at follow up (day 14±1)	244/423 (57.7%)	255/427 (59.7%)	Treatment difference −2.0% (95% CI −8.6 to 4.6 [non-inferior])
FDA primary outcome: objective (at least 20% reduction in lesion size in the absence of clinical failure) response 48 hours to 72 hours after starting treatment	354/423 (83.7%)	344/427 (80.6%)	Treatment difference 3.1% (95% CI −2.0 to 8.3 [non-inferior])
Secondary outcomes	**n=423**	**n=427**	**-**
Investigator-assessed success (cure or improved) at follow up (day 14±1)	369/423 (87.2%)	362/427 (84.4%)	Treatment difference 2.5% (95% CI −2.2 to 7.2 [non-inferior])
Investigator-assessed clinical cure at late follow up (day 21 to day 28)	287/423 (67.8%)	303/427 (71.0%)	Treatment difference −3.1% (95% CI −9.3 to 3.1 [non-inferior])
Microbiological response (documented or presumed eradication) for all gram-positive at follow up (day 14±1)	180/185 (97.3%)	163/166 (98.2%)	No statistical analysis reported
Microbiological response (documented or presumed eradication) for gram-negative infections at follow up (day 14±1)	15/15 (100.0%)	16/17 (94.1%)	No statistical analysis reported
Microbiological response (documented or presumed eradication) for all mixed gram-positive and gram-negative infections at follow up (day 14±1)	31/31 (100.0%)	28/29 (96.6%)	No statistical analysis reported
Microbiological response for all *Staphylococcus aureus* including MRSA (documented or presumed eradication) at follow up (day 14±1)	129/131 (98.5%)	114/118 (96.6%)	No statistical analysis reported
Microbiological response for MRSA (documented or presumed eradication) at follow up (day 14±1)	48/50 (96.0%)	32/33 (97.0%)	No statistical analysis reported
Safety outcomes	**n=417**	**n=425**	**-**

Any treatment-emergent adverse events	182/417 (43.6%)	167/425 (39.3%)	No statistical analysis reported
Serious adverse events	16/417 (3.8%)	17/425 (4.0%)	No statistical analysis reported
Deaths	0/417 (0.0%)	2/425 (0.5%)	No statistical analysis reported
Treatment-related adverse events	87/417 (20.9%)	89/425 (20.9%)	No statistical analysis reported
Treatment-related adverse events resulting in treatment discontinuation	5/417 (1.2%)	10/425 (2.4%)	No statistical analysis reported
Nausea	32/417 (7.7%)	19/425 (4.5%)	No statistical analysis reported
Diarrhoea	32/417 (7.7%)	14/425 (3.3%)	No statistical analysis reported

Abbreviations: CI, confidence interval; EMA, European Medicines Agency; FDA, Food and Drug Administration (US); IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

Results for clinical outcomes are presented for the intention-to-treat population (all randomised participants). Non-inferiority was concluded if the lower limit of the 2-sided 95% CI exceeded -10%. Broadly similar results were seen in the clinically evaluable population (all randomised participants who completed all activities as defined in the protocol). However, non-inferiority was not shown for investigator-assed cure at follow up or late follow up (the lower limit of the 95% CI was below the non-inferiority margin of -10%).

Analysis of microbiological outcomes was based on the microbiologically evaluable population (all randomised participants who had eligible bacterial pathogens known to cause ABSSSI at baseline and who completed all activities defined in the protocol).

The safety population included all randomised participants who received at least 1 dose of study treatment.

Results table for Pullman et al. (2017)

Outcome	Delafloxacin (IV only)	Vancomycin plus aztreonam	Analysis
Primary outcome	**n=331**	**n=329**	**-**
EMA primary outcome: investigator-assessed clinical cure at follow up (day 14±1)	172/331 (52.0%)	166/329 (50.5%)	Treatment difference 1.5% (95% CI −6.1 to 9.1 [non-inferior])
FDA primary outcome: objective response (at least 20% reduction in lesion size in the absence of clinical failure) 48 hours to 72 hours after starting treatment	259/331 (78.2%)	266/329 (80.9%)	Treatment difference −2.6% (95% CI −8.8 to 3.6 [non-inferior])
Secondary outcomes	**n=331**	**n=329**	**-**
Investigator-assessed success (cure or improved) at follow up (day 14±1)	270/331 (81.6%)	274/329 (83.3%)	Treatment difference −1.7% (95% CI −7.6 to 4.1 [non-inferior])
Investigator-assessed clinical cure at late follow up (day 21 to day 28)	233/331 (70.4%)	219/329 (66.6%)	Treatment difference 3.8% (95% CI −3.3 to 10.9 [non-inferior])
Microbiological response (documented or presumed eradication) overall at follow up (day 14±1)	175/179 (97.8%)	181/184 (98.4%)	No statistical analysis reported
Microbiological response for all *Staphylococcus aureus* including MRSA (documented or presumed eradication) at follow up (day 14±1)	115/117 (98.3%)	119/121 (98.3%)	No statistical analysis reported
Microbiological response for MRSA (documented or presumed eradication) at follow up (day 14±1)	58/58 (100%)	65/66 (98.5%)	No statistical analysis reported
Safety outcomes	**n=324**	**n=326**	**-**
Any treatment-emergent adverse events	154/324 (47.5%)	193/326 (59.2%)	No statistical analysis reported
Serious adverse events	12/324 (3.7%)	12/326 (3.7%)	No statistical analysis reported
Deaths	1/324 (0.3%)	1/326 (0.3%)	No statistical analysis reported
Treatment-related adverse events	78/324 (24.1%)	107/326 (32.8%)	No statistical analysis reported
Treatment-related adverse events resulting in treatment discontinuation	1/324 (0.3%)	8/326 (2.5%)	No statistical analysis reported
Diarrhoea	27/324 (8.3%)	10/326 (3.1%)	No statistical analysis reported

Headache	10/324 (3.1%)	25/326 (7.7%)	No statistical analysis reported
Infection	28/324 (8.6%)	25/326 (7.7%)	No statistical analysis reported
Infusion site extravasation	28/324 (8.6%)	44/326 (13.5%)	No statistical analysis reported
Nausea	24/324 (7.4%)	28/326 (8.6%)	No statistical analysis reported

Abbreviations: CI, confidence interval; IV, intravenous.

Results for clinical outcomes are presented for the ITT population (all randomised participants). Non-inferiority was concluded if the lower limit of the 2-sided 95% CI exceeded -10%. Similar results were seen in the clinically evaluable population (all randomised participants who completed all activities as defined in the protocol).

Analysis of microbiological outcomes was based on the microbiologically evaluable population (all randomised participants who had eligible bacterial pathogens known to cause ABSSSI at baseline and who completed all activities defined in the protocol).

The safety population included all randomised participants who received at least 1 dose of study treatment.

Appendix E: Literature search strategy

Database search strategies

Database: Medline

Platform: Ovid
Version: Ovid MEDLINE(R) <1946 to October 15, 2020>
Search date: 16/10/ 2020
Number of results retrieved: 33
Search strategy:

Database: Ovid MEDLINE(R) <1946 to October 15, 2020>
Search strategy:
---
1 (delafloxacin* or quofenix* or baxdela* or ABT-492 or ABT492 or RX-3341* or RX3341* or WQ-3034 or WQ3034).tw. (97)
2 exp Skin Diseases, Infectious/ (117646)
3 exp Skin/ (224957)
4 (skin or ABSSSI).tw. (471351)
5 or/2-4 (659831)
6 1 and 5 (33)

Database: Medline in-process

Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to October 13, 2020>
Search date: 15/10/2020
Number of results retrieved: 24
Search strategy:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to October 13, 2020>
Search strategy:
---
1 (delafloxacin* or quofenix).tw. (49)
2 exp Skin Diseases, Infectious/ (0)
3 exp Skin/ (0)
4 (skin or ABSSSI).tw. (80459)
5 or/2-4 (80459)
6 1 and 5 (24)

MiP search updated on 16 Oct 2020 (both sets of results imported into ESR – total 39):

Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to October 15, 2020>
Search date: 16/10/2020

Number of results retrieved: 15
Search strategy:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to October 15, 2020>
Search strategy:
---
1 (delafloxacin* or quofenix* or baxdela* or ABT-492 or ABT492 or RX-3341* or RX3341* or WQ-3034 or WQ3034).tw. (33)
2 exp Skin Diseases, Infectious/ (0)
3 exp Skin/ (0)
4 (skin or ABSSSI).tw. (53464)
5 or/2-4 (53464)
6 1 and 5 (15)

Database: Medline epubs ahead of print

Platform: Ovid
Version: Ovid MEDLINE(R) Epub Ahead of Print <October 15, 2020>
Search date: 16/10/2020
Number of results retrieved: 1
Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print <October 15, 2020>
Search strategy:
---
1 (delafloxacin* or quofenix* or baxdela* or ABT-492 or ABT492 or RX-3341* or RX3341* or WQ-3034 or WQ3034).tw. (6)
2 exp Skin Diseases, Infectious/ (0)
3 exp Skin/ (0)
4 (skin or ABSSSI).tw. (7865)
5 or/2-4 (7865)
6 1 and 5 (1)

Database: Medline daily update

Platform: Ovid
Version: Ovid MEDLINE(R) Daily Update <October 15, 2020>
Search date: 16/10/2020
Number of results retrieved: 0
Search strategy

Database: Ovid MEDLINE(R) Daily Update <October 15, 2020>
Search strategy:
---
1 (delafloxacin* or quofenix* or baxdela* or ABT-492 or ABT492 or RX-3341* or RX3341* or WQ-3034 or WQ3034).tw. (0)
2 exp Skin Diseases, Infectious/ (33)
3 exp Skin/ (113)
4 (skin or ABSSSI).tw. (215)
5 or/2-4 (287)

6 1 and 5 (0)

Database: Embase

Platform: Ovid
Version: Embase <1974 to 2020 October 15>
Search date: 16/10/2020
Number of results retrieved: 111
Search strategy:

Database: Embase <1974 to 2020 October 15>
Search strategy:
---
1 delafloxacin/ (284)
2 (delafloxacin* or quofenix* or baxdela* or ABT-492 or ABT492 or RX-3341* or RX3341* or WQ-3034 or WQ3034).tw. (240)
3 1 or 2 (349)
4 exp skin infection/ (173469)
5 exp skin/ (367108)
6 (skin or ABSSSI).tw. (715763)
7 or/4-6 (997221)
8 3 and 7 (153)
9 limit 8 to (conference abstract or conference paper or "conference review") (42)
10 8 not 9 (111)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley
Version:
CDSR – Issue 10 of 12, October 2020
CENTRAL – Issue 10 of 12, October 2020
Search date: 16th Oct 2020
Number of results retrieved: CDSR – 0 ; CENTRAL – 14.

Cochrane Library
ID Search Hits
#1 (delafloxacin* or quofenix* or baxdela* or ABT-492 or ABT492 or RX-3341* or RX3341* or WQ-3034 or WQ3034):ti,ab,kw 53
#2 MeSH descriptor: [Skin Diseases, Infectious] explode all trees 3349
#3 MeSH descriptor: [Skin] explode all trees 4377
#4 (skin or ABSSSI):ti,ab,kw 56011
#5 #2 or #3 or #4 58312
#6 #1 and #5 39
#7 "conference":pt or (clinicaltrials or trialsearch):so 499881
#8 #6 not #7 14

Database: INAHTA database

Platform: INAHTA website

Version: 16th Oct 2020
Search date: 16th Oct 2020
Number of results retrieved: 0
Search strategy:
delafloxacin* or quofenix* or baxdela* or "ABT-492"or ABT492 or RX-3341* or RX3341* or WQ-3034 or WQ3034

Trials registry search strategies

Clinicaltrials.gov

Search date: 16th Oct 2020
Number of results retrieved: 10
Search strategy: delafloxacin or quofenix or baxdela or ABT-492 or ABT492 or RX-3341 or RX3341 or WQ-3034 or WQ3034

Clinicaltrialsregister.eu

Search date: 16th Oct 2020
Number of results retrieved: 4
Search strategy: delafloxacin or quofenix or baxdela or ABT-492 or ABT492 or RX-3341 or RX3341 or WQ-3034 or WQ3034

Appendix F: Excluded studies

Study reference	Reason for exclusion
Bassetti, Matteo; Hooper, David; Tillotson, Glenn (2019) Analysis of Pooled Phase 3 Safety Data for Delafloxacin in Acute Bacterial Skin and Skin Structure Infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 68(suppl3): 233-s240	Study not prioritised (not the best available evidence)
Giordano, Philip A; Pogue, Jason M; Cammarata, Sue (2019) Analysis of Pooled Phase III Efficacy Data for Delafloxacin in Acute Bacterial Skin and Skin Structure Infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 68(suppl3): 223-s232	Study not prioritised (not the best available evidence)
Kingsley, Jeff, Mehra, Purvi, Lawrence, Laura E et al. (2016) A randomized, double-blind, Phase 2 study to evaluate subjective and objective outcomes in patients with acute bacterial skin and skin structure infections treated with delafloxacin, linezolid or vancomycin. The Journal of antimicrobial chemotherapy 71(3): 821-9	Study not prioritised (not the best available evidence)
Lan, S.-H., Lai, C.-C., Lu, L.-C. et al. (2019) Efficacy and safety of delafloxacin in the treatment of acute bacterial skin and skin structure infections: A systematic review and meta-analysis of randomized controlled trials. Infection and Drug Resistance 12: 1415-1423	Study not prioritised (not the best available evidence)
McCurdy, S, Lawrence, L, Quintas, M et al. (2017) In Vitro Activity of Delafloxacin and Microbiological Response against Fluoroquinolone-Susceptible and Nonsusceptible Staphylococcus aureus Isolates from Two Phase 3 Studies of Acute Bacterial Skin and Skin Structure Infections. Antimicrobial agents and chemotherapy 61(9)	Study not prioritised (not the best available evidence)
O'Riordan, William, Mehra, Purvi, Manos, Paul et al. (2015) A randomized phase 2 study comparing two doses of delafloxacin with tigecycline in adults with complicated skin and skin-structure infections. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 30: 67-73	Study not prioritised (not the best available evidence)
Tanvir, S.B., Qasim, S.S.B., Latimer, J. et al. (2020) The efficacy and adverse events of delafloxacin for treating acute bacterial skin and skin structure infections: A systematic review and meta-analysis. Journal of Pharmacy and Bioallied Sciences 12(5supplement1): 538-s545	Study not prioritised (not the best available evidence)