NICE advice

Antimicrobial prescribing: delafloxacin for community-acquired pneumonia

Evidence summary
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Product overview

The content of this evidence summary was up to date in August 2021. 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.

Delafloxacin (Quofenix, Menarini) is a fluoroquinolone antibiotic, which is available as a powder for infusion and a tablet. It has a marketing authorisation for community-acquired pneumonia in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment. Delafloxacin was launched in the UK in July 2020 for 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. A NICE evidence review on

delafloxacin for the treatment of ABSSSI was published in January 2021.

Advisory statement on likely place in therapy

Delafloxacin may be an option for community-acquired pneumonia in adults for exceptional cases when other antibacterial agents that are usually recommended for this are not suitable. Take account of local antimicrobial resistance and seek specialist microbiological advice. See the recommendations in the NICE guideline on antimicrobial prescribing for community-acquired pneumonia for first-choice antibiotics, antibiotics for people with suspected atypical pathogens and alternative options for people with penicillin allergy. Follow recommendations on new antimicrobials in the NICE guideline on antimicrobial stewardship: systems and processes.

Rationale

A wide range of antimicrobials, alone or in combination, are used for treating community-acquired pneumonia, depending on the severity of symptoms, risk of atypical pathogens, penicillin allergy and any microbiological results. The European public assessment report variation for delafloxacin states that delafloxacin 'does not address an unmet need in the treatment of community-acquired pneumonia, but it does provide an additional antimicrobial option.'

Evidence from 1 randomised controlled trial in 859 adults with community-acquired bacterial pneumonia treated in a non-UK setting found that delafloxacin was non-inferior to moxifloxacin for early clinical response after 96 hours of treatment. Evidence also found that delafloxacin was non-inferior to moxifloxacin for clinical response at test of cure.

Approximately 91% of the study population had a CURB-65 score of 2 or less, indicating low to moderate severity pneumonia (see Lim et al. 2003 for an explanation of the CURB-65 scale). The NICE antimicrobial prescribing guideline recommends a fluoroquinolone antibiotic (levofloxacin) as a treatment option only for high severity community-acquired pneumonia (CURB-65 score 3 to 5) in adults who have penicillin allergy.

All participants in the study had intravenous antimicrobial treatment. This could be

switched to oral treatment if clinical criteria were met. There is currently no published evidence using oral delafloxacin alone for community-acquired pneumonia. However, the intravenous infusion and tablet formulations are bioequivalent (see the summary of product characteristics for delafloxacin). There are no published clinical studies that compare delafloxacin to any other fluoroquinolones or to other classes of antimicrobials.

There are safety concerns associated with fluoroquinolone treatment. The Medicines and Healthcare products Regulatory Agency (MHRA) has recommended prescribing restrictions and precautions for fluoroquinolone antibiotics due to very rare reports of disabling and potentially long-lasting or irreversible side effects (see the Drug Safety Update March 2019). The MHRA has also advised healthcare professionals about small increased risks of aortic aneurysm and dissection, and heart valve regurgitation associated with the fluoroquinolones (see the Drug Safety Update November 2018 and the Drug Safety Update December 2020).

The NICE guideline on antimicrobial stewardship: systems and processes 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 1 multicentre double-blind randomised controlled trial (Horcajada et al. 2019) that compared intravenous delafloxacin with intravenous moxifloxacin in 859 adults with community-acquired bacterial pneumonia and a Pneumonia Patient Outcomes Research Team (PORT) risk class of II to V (scale range I to V, with V being the highest risk of mortality). In participants who met clinical criteria, treatment could be changed to the oral route after a minimum of 6 intravenous doses. The median duration of intravenous treatment was 6 days and of oral treatment was 2 days.

The study found that delafloxacin was non-inferior to moxifloxacin for early clinical response, assessed 96 hours (±24 hours) after the start of treatment (primary outcome and US Food and Drug Administration primary outcome). Early clinical response was defined as improvement in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum, dyspnoea and no worsening

of the other symptoms. This was seen in 383 of 431 (88.9%) of participants in the delafloxacin group compared with 381 of 428 (89.0%) in the moxifloxacin group (difference −0.2%, 95% confidence interval [CI] −4.4% to 4.1%).

Clinical response (defined as success, failure or indeterminate) at test of cure (5 to 10 days after the last dose of study drug) was the European medicines agency primary outcome and a secondary outcome in the Horcajada et al. (2019) study. In the study, 390 out of 431 (90.5%) participants in the delafloxacin group had clinical success compared with 384 of 428 (89.7%) participants in the moxifloxacin group (difference 0.8%, 95% CI −3.3% to 4.8%). The European public assessment report (EPAR) variation for delafloxacin concluded that delafloxacin was non-inferior to moxifloxacin for clinical response at test of cure, the EPAR variation used a slightly different population (modified intention-to-treat) than the study.

Streptococcus pneumoniae was the most common baseline pathogen (found in 43.5% of people with a baseline pathogen identified). *Haemophilus influenzae* and *Legionella pneumophila* were both identified in 11.9% of participants with a baseline pathogen and *Staphylococcus aureus* was identified in 11.0%.

Treatment-emergent adverse events were seen in 131 of 429 (30.5%) participants given delafloxacin and 112 of 427 (26.2%) participants given moxifloxacin in Horcajada et al. (2019). In the delafloxacin group, 15 out of 429 (3.5%) participants stopped treatment due to a treatment-emergent adverse event compared with 7 out of 427 (1.6%) participants in the moxifloxacin group. No statistical analyses were reported for safety data.

The summary of product characteristics (SPC) for delafloxacin lists the following common adverse reactions (seen in between 1 in 10 and 1 in 100 people): fungal infection, headache, diarrhoea, vomiting, nausea, pruritus, infusion site reaction and hypertransaminasaemia (raised liver transaminases).

There are safety concerns associated with fluoroquinolone treatment. The MHRA has recommended prescribing restrictions and precautions for fluoroquinolone antibiotics due to very rare reports of disabling and potentially long-lasting or irreversible side effects (see the Drug Safety Update March 2019). The MHRA has also advised healthcare professionals on a small increased risk of aortic aneurysm and dissection (see the Drug Safety Update November 2018) and a small risk of heart valve regurgitation (see the Drug Safety Update December 2020) associated with the fluoroquinolones.

The SPC includes several warnings and precautions for use which reflect the safety profile of the fluoroquinolones. See the SPC for delafloxacin for full details on contraindications, warnings and precautions for use.

Limitations of the evidence

The participants in the study had a mean age of 60, with approximately 45% of participants 65 years and older. The SPC for delafloxacin states that in the study, 90.7% of the population had a CURB-65 score of 2 or less, indicating low to moderate severity pneumonia. Therefore, the study population may not be representative of people with high severity community-acquired pneumonia. The NICE antimicrobial prescribing guideline on community-acquired pneumonia recommends a fluoroquinolone antibiotic (levofloxacin) as a treatment option only for high severity community-acquired pneumonia in adults who have penicillin allergy. In addition, the NICE guideline recommends that oral antibiotics should be given first line if the person can take oral medicines, and the severity of their condition does not require intravenous antibiotics. Specialists who commented on this evidence review raised that it was unclear why study participants with mild to moderate community- acquired pneumonia had intravenous treatment when an oral preparation is available. They also noted that the duration of intravenous treatment was longer than it would usually be in UK practice.

Delafloxacin has been compared with moxifloxacin. There are no published clinical studies that compare delafloxacin to any other fluoroquinolones or to other classes of antimicrobials. There is currently no published evidence using oral delafloxacin alone for community-acquired pneumonia. However, the intravenous infusion and tablet formulations are bioequivalent (see the SPC for delafloxacin).

The study was conducted in 88 centres in 18 countries. None of the centres were in the UK and it's unclear if the study population compares with the UK population.

Person-centred factors

Delafloxacin infusion is administered intravenously every 12 hours, over 1 hour. The NICE guideline on antimicrobial prescribing for community-acquired pneumonia recommends that if intravenous antibiotics are given there should be a review by 48 hours and consideration given to switching to oral antibiotics if possible.

The SPC states 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. Switching to oral treatment is likely to be preferable to people in terms of ease of administration and convenience compared with ongoing intravenous treatment.

Antimicrobial resistance

Delafloxacin is a new antimicrobial and therefore data on resistance and impact on clinical practice in the UK are limited. Information on resistance can be found in Public Health England's antimicrobial resistance local indicators.

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 (see the BNF information on delafloxacin).

Delafloxacin is given every 12 hours and the recommended total duration of treatment is 5 to 10 days. The recommended antimicrobial treatment duration in the NICE antimicrobial prescribing guideline on community-acquired pneumonia is 5 days, which would cost £615.

The cost of 1 levofloxacin 500 mg tablet is £2.09 (see the Drug Tariff; July 2021) and the cost of levofloxacin 500 mg in 100 ml intravenous infusion is £4.00 for 1 bag (see the BNF information on levofloxacin). The recommended dosage of levofloxacin in the NICE antimicrobial prescribing guideline on community-acquired pneumonia is 500 mg twice a day orally or intravenously for 5 days. This would cost £20.86 for oral treatment and £40.00 for intravenous treatment.

See the full evidence review for more information.

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