Delafloxacin

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.2. Watch group antibiotics

ATC codes: J01MA23

Indication	Methicillin resistant Staphylococcus aureus ICD11 code: MG51.00
INN	Delafloxacin
Medicine type	Device
Antibiotic groups	WATCH
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 300 mg lyophilized powder for injection **Oral > Solid:** 450 mg
EML status history	Application rejected in 2019 (TRS 1021)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Read more about patents.
Wikipedia	Delafloxacin
DrugBank	Delafloxacin

Expert Committee recommendation

The Expert Committee did not recommend the addition of delafloxacin to the EML. The Committee noted that although delafloxacin has demonstrated activity against some MRSA strains ranked as “high priority” on the WHO priority pathogens list, effective alternatives are currently available on the EML. In addition, delafloxacin was not associated with greater activity against “critical priority” pathogens compared to other, older fluoroquinolones currently available on the Model List. The Expert Committee agreed with the EML Antibiotic Working Group’s recommendation that this antibiotic should be classified in the AWaRe Watch group.

Background

The application requested the inclusion of delafloxacin on the complementary list of the EML as a last-resort treatment option for infections due to multidrug-resistant organisms (MRDOs). Delafloxacin had not previously been considered for inclusion on the EML. It is a new fluoroquinolone which, compared to the older molecules of this class, has activity against methicillin-resistant S. aureus (MRSA) (1, 2). It has been approved for treatment of skin and soft tissue infections based on two Phase III multicentre, double-blind non-inferiority trials (3, 4).

Public health relevance

Antibiotic-resistant bacteria are a significant threat to public health, both in HICs as well as LMICs (5–7). A recent

study estimated that infections with antibiotic- resistant bacteria were responsible for approximately 33 000 attributable deaths in Europe in 2015 (5). Fewer data are available for LMICs, but a retrospective study in ten hospitals in India found that resistant pathogens were associated with two to three times higher mortality than infections with susceptible strains after adjusting for several confounders (6). Over the past decade there has been increasing spread of multidrugresistant Gram-negative pathogens such as carbapenemase producing Enterobacteriaceae (8). The Global Antimicrobial Resistance Surveillance System (GLASS) report published in 2018 found high levels of carbapenem resistance in Enterobacteriaceae and non-fermenters in many of the LMICs providing data for the report (6). The 2015 WHO Global action plan on antimicrobial resistance calls for the development of new antimicrobial medicines (7). To provide a framework for this endeavour, in 2017 WHO published a priority list of antibiotic-resistant bacteria (9). “Priority 1: critical” category includes four types of pathogens, all of which are Gram-negative: carbapenem resistant Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacteriaceae; and third-generation cephalosporin-resistant Enterobacteriaceae (10).

Benefits

In the two Phase III trials in adult patients with acute bacterial skin and skin structure infections, delafloxacin fulfilled criteria for non-inferiority compared to linezolid and vancomycin/aztreonam respectively (3, 4). In respective trials, one third and one fourth of patients had infections due to MRSA. A trial comparing delafloxacin to moxifloxacin (or linezolid in the case of confirmed MRSA) in patients with community-acquired pneumonia (NCT02679573) has been completed in 2018 but results have not yet been published.

Harms

A review of the safety data of the two Phase III non-inferiority RCTs and additional Phase I and II trials showed few discontinuations (<1%) due to treatment-related adverse events (3, 4, 11). The proportion of patients with AEs was similar to the proportion observed in the comparator arms. No fluoroquinolone-specific AE such as tendinitis or neuropathy were observed in the delafloxacin arm. Gastrointestinal events (notably diarrhoea), headache and infusion site pain were the most frequently reported AEs. Adverse events associated with fluoroquinolones (tendinitis, myopathy, dysglycaemia, neuropathy, neurotoxicity) were not more frequent when compared with vancomycin/aztreonam with the caveat that the combined Phase III trials only included 1492 patients and rare, potentially severe events were unlikely to be detected. There are no data for use of delafloxacin in children, and similar to other fluoroquinolones it is not recommended for use in patients younger than 18 years.

Additional evidence

Delafloxacin has been suggested as a treatment option for gonorrhoea with good in vitro activity even against strains with reduced susceptibility to ciprofloxacin (12). The results of an open-label, multicentre study with 460 participants with uncomplicated gonorrhoea was recently published (13). Patients were randomized (2:1) to either a single oral dose of 900 mg of delafloxacin or 250 mg of intramuscular ceftriaxone. Delafloxacin did not fulfil the predefined criteria for non-inferiority for the primary outcome urogenital cure (85.1% (194/228) vs 91.0% (91/100); 95%CI −13.18% to 1.36%; the lower bound of the CI thus exceeding the pre-specified −10% non-inferiority margin).

Cost / cost effectiveness

Approximately US$ 260 per day.

WHO guidelines

There are no available WHO guidelines for the treatment of infections due to MDROs. Delafloxacin is not mentioned in the 2016 WHO Guidelines for the treatment of Neisseria gonorrhoeae (issued before the availability of delafloxacin) (14).

Availability

Delafloxacin is approved in the United States and Europe for the treatment of acute bacterial skin and skin structure infections.

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2. Saravolatz LD, Stein GE. Delafloxacin: A New Anti-methicillin-resistant Staphylococcus aureus Fluoroquinolone. Clin Infect Dis. 2019;68(6):1058-62. Clin Infect Dis. 2019;68(6):1058-62.
3. Pullman J, Gardovskis J, Farley B, Sun E, Quintas M, Lawrence L, et al. 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. J Antimicrob Chemother. 2017;72(12):3471–80.
4. O'Riordan W, McManus A, Teras J, Poromanski I, Cruz-Saldariagga M, Quintas M, et al. 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. Clin Infect Dis. 2018;67(5):657–66.
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6. Gandra S, Tseng KK, Arora A, Bhowmik B, Robinson ML, Panigrahi B, et al. The mortality burden of multidrug-resistant pathogens in India: a retrospective observational study. Clin Infect Dis. 2019; 69(4): 563–570.
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11. Lodise T, Corey R, Hooper D, Cammarata S. Safety of Delafloxacin: Focus on Adverse Events of Special Interest. Open Forum Infect Dis. 2018;5(10):ofy220.
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13. Hook EW, 3rd, Golden MR, Taylor SN, Henry E, Tseng C, Swerdlow J, et al. Efficacy and safety of single dose oral delafloxacin compared with intramuscular ceftriaxone for uncomplicated gonorrhea treatment: an open-label, non-inferiority, Phase 3, multicenter, randomized study. Sex Transm Dis. 2019 (epub ahead of print).
14. Guidelines for the treatment of Neisseria gonorrhoeae. Geneva: World Health Organization; 2016.

