Omadacycline

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 > 6.2.3. Reserve group antibiotics

ATC codes: J01AA15

Indication	Methicillin resistant Staphylococcus aureus ICD11 code: MG51.00
INN	Omadacycline
Medicine type	Chemical agent
Antibiotic groups	R RESERVE
List type	Complementary
Formulations	Parenteral > General injections > IV: 100 mg lyophilized powder for injection Oral > Solid: 300 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	Omadacycline
DrugBank	Omadacycline

Expert Committee recommendation

The Expert Committee did not recommend the addition of omadacycline to the EML. The Committee considered that although omadacycline demonstrates activity against both Gram-positive and Gram-negative pathogens, including MRSA, available data for its effectiveness and safety are currently limited. The Committee noted the finding of potentially increased mortality associated with omadacycline in one RCT of patients with community-acquired pneumonia. The Expert Committee agreed with the EML Antibiotic Working Group's recommendation that omadacycline be classified in the AWaRe Reserve group.

Background

The application requested the inclusion of omadacycline on the complementary list of the EML as a last-resort treatment option for infections due to multidrugresistant organisms (MDROs). Omadacycline had not previously been considered for inclusion on the EML. Omadacycline, a recently approved tetracycline antibiotic, has a broad spectrum of activity against many Gram-positive and Gram-negative pathogens, including methicillin-resistant Staphylococcus aureus (MRSA) (1). MRSA is ranked as a "high priority" pathogen on the WHO priority pathogens list (2).

Public health relevance

Antibiotic-resistant bacteria are a significant threat to public health, both in HICs as well as LMICs (3–5). A recent study estimated that infections with antibiotic- resistant bacteria were responsible for approximately 33 000 attributable deaths in Europe in 2015 (3). 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 (4). Over the past decade there has been increasing spread of multidrugresistant Gram-negative pathogens such as carbapenemase producing Enterobacteriaceae (6). 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 (4). The 2015 WHO Global action plan on antimicrobial resistance calls for the development of new antimicrobial medicines (5). To provide a framework for this endeavour, in 2017 WHO published a priority list of antibiotic-resistant bacteria (2). "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 (7).

Benefits

Several RCTs of omadacycline had been conducted or were currently ongoing, but at the time of writing the application the results had not yet been published in the peer-reviewed literature. ■ Omadacycline versus moxifloxacin for the treatment of communityacquired bacterial pneumonia (CABP) (NCT02531438), Phase III, double-blind, multicentre non-inferiority RCT (2015–2017) in 774 adult patients with CABP. Primary outcome: Number of participants with early clinical response 81.1% vs 82.7% (difference −1.6 percentage points, 95%CI −7.1 to 3.8). ■ Omadacycline versus linezolid for the treatment of acute bacterial skin and skin structure infections (ABSSSI) (NCT02378480), Phase III, double-blind, multicentre non-inferiority RCT (2015-2016): results not yet available. ■ Oral omadacycline versus oral linezolid for the treatment of ABSSSI (NCT02877927), Phase III, double-blind, multicentre noninferiority RCT (2016–2017) in 735 adult patients with ABSSSI, Primary outcome: Early clinical response 87.5% vs 82.5% (difference +5.0 percentage points, 95%CI −0.2 to 10.3). ■ Oral omadacycline versus oral nitrofurantoin for the treatment of cystitis (NCT03425396): trial still recruiting. The results of NCT02531438 and NCT02378480 have since been published (see additional evidence).

Harms

See additional evidence.

Additional evidence

Two noninferiority RCTs of omadacycline in adults with CABP and ABSSSI were published in February 2019. A double-blind, noninferiority (10 percentage point margin) RCT allocated adults with CABP to either omadacycline or moxifloxacin with possible transition to the oral equivalent after three days for a total treatment duration of between 7 and 14 days. The primary outcome was early clinical response (according to predefined criteria) at 72 to 120 hours. Omadacycline fulfilled criteria for noninferiority for early clinical response (81.1% vs 82.7%, difference, −1.6 percentage points; 95%CI −7.1 to 3.8) (8). The frequency of adverse events (AE) was similar in both groups, with gastrointestinal side effects being the most commonly observed AE (10.2% vs 18.0%). There was a slight imbalance in mortality with eight deaths occurring in the omadacycline group versus four in the moxifloxacin group, disproportionately affecting patients with more severe pneumonia. A second double-blind, noninferiority (10 percentage point margin) trial, randomly assigned adults with ABSSSI to treatment with omadacycline or linezolid with possible transition to the oral equivalent after three days for a total treatment duration between 7 and 14 days. The primary outcome was early clinical response (48–72 hours), defined as survival, absence of rescue antibiotic therapy and ≥ 20% reduction in lesion size. Omadacycline fulfilled criteria for non-inferiority for early clinical response (84.8% vs 85.5%, difference −0.7 percentage points, 95%CI −6.3 to 4.9) (9). The frequency of adverse events was similar in both groups, with gastrointestinal side effects being the most commonly observed AE (18.0% vs 15.8%).

Cost / cost effectiveness

No information regarding costs available. Few data are available regarding the cost-effectiveness of omadacycline. A modelling study estimated potential cost savings with omadacycline treatment compared with inpatient IV vancomycin treatment in patients with acute bacterial skin and skin-structure infections by shifting care to the outpatient setting due to the availability of an oral formulation of omadacycline (10). The study assumed that a large proportion (50%) of patients would continue with IV vancomycin (rather than a switch to an oral agent), limiting applicability to 'real-world' scenarios. It was noted that the first author of this study was an employee of the pharmaceutical company producing omadacycline.

WHO guidelines

There are no available WHO guidelines for the treatment of infections due to multidrug-resistant organisms.

Availability

The drug has been approved for the treatment of community acquired bacterial pneumonia and acute bacterial skin and skin structure infections in the United States (11).

1. Montravers P, Tran-Dinh A, Tanaka S. The role of omadacycline in skin and soft tissue infections. Curr Opin Infect Dis. 2018;31(2):148–54.
2. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017. Available from: https://apps.who.int/iris/handle/10665/311820, accessed 30 October 2019.
3. Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019; 19(1):56–66.
4. 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.
5. Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015. Available from: https://apps.who.int/iris/handle/10665/311820, accessed 30 October 2019.
6. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence. 2017;8(4):460–9.
7. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318–27.
8. Stets R, Popescu M, Gonong JR, Mitha I, Nseir W, Madej A, et al. Omadacycline for CommunityAcquired Bacterial Pneumonia. N Engl J Med. 2019;380(6):517–27.
9. O'Riordan W, Green S, Overcash JS, Puljiz I, Metallidis S, Gardovskis J, et al. Omadacycline for Acute Bacterial Skin and Skin-Structure Infections. N Engl J Med. 2019;380(6):528–38.
10. LaPensee K, Lodise T. Potential Cost-Savings with Once-Daily Aminomethylcycline Antibiotic versus Vancomycin in Hospitalized Patients with Acute Bacterial Skin and Skin Structure Infections. Am Health Drug Benefits. 2018;11(9):449–59.
11. Markham A, Keam SJ. Omadacycline: First Global Approval. Drugs. 2018;78(18):1931–7.