Plazomicin

Essential medicine status

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.3. Reserve group antibiotics

ATC codes: J01GB14

Indication	Carbapenem resistant Escherichia coli ICD11 code: MG50.24
INN	Plazomicin
Medicine type	Chemical agent
Antibiotic groups	RESERVE
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 500 mg per 10 mL
EML status history	First added in 2019 (TRS 1021)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Plazomicin
DrugBank	Plazomicin

Expert Committee recommendation

The Expert Committee recommended the inclusion of plazomicin on the complementary list of the EML for the treatment of infections caused by carbapenem-resistant organisms which are pathogens classified as “critical priority” in the WHO Priority Pathogen List. The Committee agreed with the EML Antibiotic Working Group’s recommendation that this antibiotic should be classified in the AWaRe Reserve group (Section 6.2.3). The Committee recommended further collaboration between relevant stakeholders to design and implement strategic public health orientated studies that will help to inform the choice of optimal single or combinations of both novel and older antibiotics for adults and children in different settings, with the goal of improving clinical outcomes, minimizing toxicity and reducing selection of resistance.

Background

Plazomicin had not previously been considered for inclusion on the EML. Plazomicin is a next-generation aminoglycoside which is not affected by many aminoglycoside-modifying enzymes of Enterobacteriaceae that inactivate other types of aminoglycosides (1, 2). This makes it a potentially useful drug for the treatment of carbapenemase-producing Enterobacteriaceae since aminoglycosides are not affected by carbapenemase production (metallo-betalactamases may be an exception since they often are associated with genes for methylases affecting and inactivating all types of aminoglycosides, including plazomicin).

Public health relevance

Antibiotic-resistant bacteria are a significant threat to public health, both in high-income as well as low- and middle-income countries (LMIC) (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 LMIC, but a retrospective study in ten hospitals in India found that resistant pathogens were associated with 2-3 times higher mortality than infections with susceptible strains after adjusting for several confounders (4). Over the last decade there has been increasing spread of

multidrug-resistant 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 – the WHO Priority Pathogens List (7). “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 (8).

Benefits

See additional evidence.

Harms

Like all aminoglycosides plazomicin is potentially nephrotoxic. Increases in serum creatinine levels of 0.5 mg or more per deciliter (≥40 µmol per litre) above baseline occurred in 7.0% of patients in the plazomicin group and in 4.0% in the meropenem group in the non-inferiority trial comparing plazomicin to meropenem for patients with complicated urinary tract infections (see additional evidence) (9).

Additional evidence

Results of a non-inferiority trial comparing plazomicin to meropenem for patients with complicated urinary tract infections (UTIs) were published in January 2019 (9). 609 patients with a diagnosis of complicated UTI were randomly allocated 1:1 to IV plazomicin or meropenem with the option for oral step-down treatment after at least 4 days of IV treatment with a total treatment duration of 7 to 10 days of therapy. The primary outcome was “composite cure” (clinical cure and microbiologic eradication) at day 5, and 15 to 19 days after treatment start in the microbiologic modified intention-to-treat population. Plazomicin fulfilled the non-inferiority criteria for both endpoints (with a 15% prespecified non-inferiority margin): 88.0% (168/191) vs 91.4% (180/197) (difference, –3.4 percentage points; 95% CI, –10.0 to 3.1) and 81.7% (156/191) versus 70.1% (138/197) (difference, 11.6 percentage points; 95% CI, 2.7 to 20.3) respectively.

Cost / cost effectiveness

US: Dosing is weight-based but a dose of 1000mg for a 70 kg person with good renal function is reported to be approximately 750 USD. No data regarding the cost-effectiveness of plazomicin compared to other treatment options are available.

WHO guidelines

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

Availability

Plazomicin is approved by the FDA for patients 18 years of age or older for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis caused by the following susceptible microorganism(s): Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Enterobacter cloacae. An application has been filed in Europe by the producing company but is currently pending.

Other considerations

The Committee noted that there was very limited clinical trial evidence of the efficacy of recently approved antibiotics against carbapenem-resistant infections, with activity based on small sample size studies including heterogenous populations. The Committee was concerned that the current regulatory approval process for novel agents effective against the WHO Priority Pathogen List “critical priority” pathogens does not adequately inform the urgent public health need for clear evidence-based guidance on the optimal management of these infections, which are associated with high mortality.

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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 populatio

n-level modelling analysis. Lancet Infect Dis. 2018.
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. 2018.
5. World Health Organization. Global Action Plan on Antimicrobial Resistance. 2015.
6. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence. 2017;8(4):460-9.
7. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017(WHO/EMP/IAU/2017.12). (Licence: CC BY-NC-SA 3.0 IGO). Available from https://apps.who.int/iris/handle/10665/311820. .
8. 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.
9. Wagenlehner FME, Cloutier DJ, Komirenko AS, Cebrik DS, Krause KM, Keepers TR, et al. Once-Daily Plazomicin for Complicated Urinary Tract Infections. N Engl J Med. 2019;380(8):729-40.