Indication: Carbapenem-resistant Pseudomonas aeruginosa

ICD11 code: MG50.80

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.

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).

Background

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
Benefits

Harms

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.