Ceftolozane + tazobactam

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: J01DI54

Indication	Carbapenem-resistant Pseudomonas aeruginosa ICD11 code: MG50.80
INN	Ceftolozane + tazobactam
Medicine type	Chemical agent
Antibiotic groups	R RESERVE
List type	Complementary
Formulations	Parenteral > General injections > IV: 1 g + 0.5 g powder for injection
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	Ceftolozane + tazobactam
DrugBank	Ceftolozane Tazobactam

Expert Committee recommendation

The Expert Committee did not recommend the addition of ceftolozane + tazobactam to the EML. The Committee noted that although ceftolozane + tazobactam is active against some strains of carbapenem-resistant P. aeruginosa, it lacks activity against carbapenemase-producing Enterobacteriaceae, which is more prevalent in the community and represents a greater public health threat. Alternative antibiotics are included on the list that are effective against carbapenem-resistant P. aeruginosa. The Committee agreed with the EML Antibiotic Working Group's recommendation that this antibiotic should be classified in the AWaRe Reserve group.

Background

The application requested the inclusion on the EML of ceftolozane + tazobactam as a last-resort treatment option for infections due to multi-drug resistant organisms (MDROs). Ceftolozane + tazobactam is the combination of a new cephalosporin with a structure similar to ceftazidime with a beta-lactam inhibitor that has been in clinical use for decades (tazobactam). Ceftolozane + tazobactam retains in vitro activity against some strains of multidrug-resistant P. aeruginosa and against Enterobacteriaceae producing ESBL. It only has limited activity against Grampositive pathogens and anaerobes (1).

Public health relevance

Antibiotic-resistant bacteria are a significant threat to public health, both in HICs as well as LMICs (2–4). A recent study estimated that infections with antibiotic-resistant bacteria were responsible for approximately 33 000 attributable deaths in Europe in 2015

(2). 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 (3). Over the past decade there has been increasing spread of multidrugresistant Gram-negative pathogens such as carbapenemase producing Enterobacteriaceae (5). 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 (3). The 2015 WHO Global action plan on antimicrobial resistance calls for the development of new antimicrobial medicines (4). To provide a framework for this endeavour, in 2017 WHO published a priority list of antibiotic-resistant bacteria (6). The "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

Ceftolozane + tazobactam has been assessed in two non-inferiority RCTs, one for cUTI and one for cIAI (8, 9). Of note, in the cUTI trial levofloxacin was used as comparator agent, a highly debatable choice given that resistance to levofloxacin in Gram-negatives isolated in urine cultures at baseline was nearly 10 times more prevalent at baseline (2.7% for C+T vs 26.7% for levofloxacin) (9). An RCT in ventilator-associated pneumonia is currently being conducted (ClinicalTrials.gov Identifier: NCT01853982). A retrospective cohort study in of 101 patients treated with ceftolozane + tazobactam in 22 Italian centres for a variety of infections causes by P. aeruginosa, including 51% of extensively drug-resistant (XDR) strains, showed overall clinical success of 83.2% and a good safety profile (10). A secondary analysis of the 150 of 1346 (11.1%) patients with ESBL-producing organisms in the original two RCTs reported high clinical cure rates with ceftolozane + tazobactam (overall 97.4%), better than the comparators (82.6% for levofloxacin (cUTI only) and 88.5% for meropenem (cIAI only)) (11). The major methodological limitations of these studies mean, however, that the data have to be interpreted with caution. Data for children are scarce and no specific recommendations regarding use in the paediatric population can be made (12, 13).

Harms

In the two non-inferiority Phase III RCTs published so far adverse events (AE) occurred with similar frequency in the ceftolozane + tazobactam and comparator groups with headache and gastrointestinal symptoms being the most frequent AE (8, 9).

Cost / cost effectiveness

United States: About US$ 1140 for 10 vials (1/0.5g) => about US$ 340 per day A decision-analytic Monte Carlo simulation model aimed to assess the costs of empiric treatment with ceftolozane + tazobactam versus or piperacillin/ tazobactam in hospitalized adults with cUTI due to Gram-negative pathogens in the United States setting. The study co-authored by multiple employees of the producer of ceftolozane + tazobactam estimated an incremental costeffectiveness ratio of US$ 6128 per QALY (14). A similar study in the United Kingdom, for patients with cIAI estimated an incremental cost-effectiveness ratio of £ 4350 per QALY in favour of ceftolozane + tazobactam (with metronidazole) compared to piperacillin/tazobactam (15).

WHO guidelines

There are no available WHO guidelines for the treatment of infections due to MDROs.

Availability

Ceftolozane + tazobactam has been approved for the treatment of cIAI and cUTI, including acute pyelonephritis in the United States and European Union.

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3. 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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