Meropenem + vaborbactam

Codes ATC: J01DH52

Indication	Carbapenem-resistant Pseudomonas aeruginosa Code ICD11: MG50.80
INN	Meropenem + vaborbactam
Type de médicament	Chemical agent
Groupes d'antibiotiques	R RESERVE
Type de liste	Liste complémentaire
Formulations	**Parenteral > General injections > IV:** 1 g in vial + 1 g in vial powder for injection
Historique des statuts LME	Ajouté pour la première fois en 2019 (TRS 1021)
Sexe	Tous
Âge	Adolescents et adultes
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Lire la suite sur les brevets.
Wikipédia	Meropenem + vaborbactam
DrugBank	Meropenem, Vaborbactam

Recommandation du comité d'experts

The Expert Committee recommended the inclusion of meropenem + vaborbactam on the complementary list of the EML of meropenem + vaborbactam 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.

Contexte

Meropenem + vaborbactam is a combination of the carbapenem meropenem with the non-suicidal cyclic boronic acid–based β-lactamase inhibitor vaborbactam (1, 2). Vaborbactam inhibits Ambler class A and C β-lactamases of which KPC-carbapnemases and some extended spectrum beta-lactamases are currently the clinically most relevant examples. Metallo-β-lactamases (e.g. NDM, VIM) and class D β-lactamases are not inhibited by vaborbactam.

Pertinence pour la santé publique

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).

Bénéfices

As of December 2018, meropenem + vaborbactam was assessed in two phase 3 randomized controlled trials (9, 10). The TANGO I trial showed non-inferiority of meropenem + vaborbactam versus piperacillin + tazobactam for the treatment of complicated urinary tract infections (infection with a pathogen resistant to standard antibiotics was not an inclusion criterion) (9). The TANGO II trial, a phase 3, multicentre, multinational, open-label randomized clinical trial, compared meropenem + vaborbactam to the best available therapy (BAT; often a combination of antibiotics) in patients with a variety of infections caused by carbapenem resistant Enterobacteriaceae and showed decreased 28-day all-cause mortality (15.6% (5/32) vs. BAT 33.3% (5/15)) with meropenem + vaborbactam compared to BAT with a wide confidence interval given the small sample size (95% CI of difference, - 44.7% to 9.3%) (10).

Torts

In the TANGO I and TANGO II trials adverse events were similar in the meropenem + vaborbactam group and in the comparator group.

Preuves supplémentaires

N/A

Rapport coût/efficacité

US: about 200 USD for 1g/1 g, equivalent to 1200 USD for an average daily dose of 2 g + 2 g every 8 hours. No data about cost-effectiveness are available.

Directives de l'OMS

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

Disponibilité

Meropenem + vaborbactam is approved by the FDA for patients 18 years of age and older with complicated urinary tract infections (cUTI), including pyelonephritis. The EMA approved its use in the European Union for • Complicated urinary tract infection, including pyelonephritis, a sudden and severe infection causing the kidneys to swell and which may permanently damage them; • Complicated intra-abdominal infection; • Hospital-acquired pneumonia, including ventilator associated pneumonia; • Bacteria in the blood associated with any of the infections listed above; • Infections due to aerobic Gram-negative organisms in adults with limited treatment

options.

Autres considérations

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.

1. Cho JC, Zmarlicka MT, Shaeer KM, Pardo J. Meropenem/Vaborbactam, the First Carbapenem/beta-Lactamase Inhibitor Combination. Ann Pharmacother. 2018;52(8):769-79.
2. Lee YR, Baker NT. Meropenem-vaborbactam: a carbapenem and beta-lactamase inhibitor with activity against carbapenem-resistant Enterobacteriaceae. Eur J Clin Microbiol Infect Dis. 2018;37(8):1411-9.
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. 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. Kaye KS, Bhowmick T, Metallidis S, Bleasdale SC, Sagan OS, Stus V, et al. Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection: The TANGO I Randomized Clinical Trial. JAMA. 2018;319(8):788-99.
10. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, Mathers AJ, Bassetti M, Vazquez J, et al. Effect and Safety of Meropenem-Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. Infectious diseases and therapy. 2018;7(4):439-55.