Meropenem + vaborbactam

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

ATC codes: J01DH52

Indication	Carbapenem-resistant Pseudomonas aeruginosa ICD11 code: MG50.80
INN	Meropenem + vaborbactam
Medicine type	Chemical agent
Antibiotic groups	R RESERVE
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 1 g in vial + 1 g in vial powder for injection
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	Meropenem + vaborbactam
DrugBank	Meropenem, Vaborbactam

Expert Committee recommendation

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.

Background

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.

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

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).

Harms

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

Additional evidence

N/A

Cost / cost effectiveness

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.

WHO guidelines

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

Availability

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.

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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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.
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