Note on use of Meropenem-vaborbactam from Antimicrobial Resistance Infection Control Division of HPSC (December 2019)

For: Consultant Microbiologists, Infectious Disease Physicians, Antimicrobial Pharmacists

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Recommendation

Meropenem-vaborbactam should be used only on the recommendation of a Consultant Microbiologist or Infectious Disease Physician.

It may be considered for use in treatment of patients with (a) laboratory confirmed infection with KPC producing CPE or (b) patients with clinical evidence of CPE infection where there is reason to suspect infection with KPC producing CPE because the patient is colonised with KPC producing CPE. Use of meropenem-vaborbactam should normally be guided by laboratory confirmation of susceptibility to meropenem-vaborbactam before initiation of therapy or as soon as possible thereafter.

Meropenem-vaborbactam may be particularly suitable for treatment of patients with (a) confirmed or suspected infection with KPC producing CPE in whom the combination of ceftazidime-avibactam should be avoided for example because of a history of immediate type hypersensitivity to penicillins or (b) with confirmed or suspected infection with KPC3 producing CPE or (c) confirmed or suspected infection with KPC demonstrating ceftazidime-avibactam resistance and meropenem-vaborbactam susceptibility.

Background

Meropenem-vaborbactam was recently licensed and is now available in Ireland. Meropenem-vaborbactam will be considered by the NCPE and the HSE-PCRS prior to a reimbursement recommendation. This does not prevent a hospital obtaining the agent for an individual patient where it is considered essential for their care. It is a combination of meropenem with vaborbactam. Vaborbactam is an inhibitor of KPC carbapenemase.

The meropenem-vaborbactam combination is therefore active against Enterobacterales resistant to meropenem by virtue of production of the KPC enzyme. Vaborbactam does not inhibit the OXA, NDM, VIM or IMP enzymes therefore the combination is not intended for use to treat infection with OXA, NDM, VIM or IMP producing CPE.

The principle clinical evidence to support the use of meropenem-vaborbactam is from two phase 3 randomised controlled trials (Tango I and Tango II). Tango I examined the effect of meropenem-vaborbactam versus piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection (cUTI). This study was not designed to evaluate meropenem-vaborbactam for treating carbapenem-resistant pathogens.

Tango II was an open-label, randomised trial of meropenem with vaborbactam (2 g/2 g IV over 3 hours, every 8 hours). Trial participants were adults with cUTI, acute pyelonephritis, complicated intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), or bacteraemia suspected or documented to be caused by carbapenem-resistant Enterobacterales. The control arm is referred to by the authors as "best available therapy" (BAT). This corresponds in fact to a very heterogeneous group of treatment regimens (agent and dose) chosen on a case by case basis by the treating physician. There were 15 patients in the control arm of the primary analysis population. Four of the 15 were on single agent therapy with one of the four on ceftazidime-avibactam. Ten patients received dual (n=7), triple (n=1) or quadruple therapy (n=2) based on polymyxin, carbapenem, aminoglycoside, or tigecycline. One patient received dual therapy with ceftazidime-avibactam but was excluded from data analysis as only monotherapy was permitted as per protocol. Tango II was a descriptive study only and no formal power or sample size calculations were performed. In comparison to physician choice of treatment meropenem-vaborbactam demonstrated improved cure (33% vs. 65%), lower mortality (33% vs. 15%) and less adverse events (44% vs. 24%). However numbers in the study are low and the description of some of the physician chosen treatment regimens would not be universally considered best available therapy. Note that it is not possible, based on this study, to make an assessment of the relative effectiveness of meropenem-vaborbactam compared with ceftazidime-avibactam.

There is a meropenem-vaborbactam monograph included in the National CPE Expert Group Guideline on the Treatment of Infection with Carbapenem Resistant Organisms April 2019, page 30. The notable differences between the meropenem-vaborbactam SmPC available at www.medicines.ie and the National guideline monograph are highlighted below:

1. Differences in dose recommendations for renal impairment – follow SmPC information included below

Table 2: Recommended intravenous doses for patients with a CrCl ≤39 ml/min[1]

CrCl (ml/min)[1]	Recommended Dosage Regimen[2]	Dosing Interval	Infusion Time
20 to 39	1 g/1 g	Every 8 hours	3 hours
10 to 19	1 g/1 g	Every 12 hours	3 hours
Less than 10	0.5 g/0.5 g	Every 12 hours	3 hours

[1] As calculated using the Cockcroft-Gault formula
[2] Refer to Table 1 for the recommended duration of treatment

2. As per SmPC recommendation monitor hepatic function due to the risk of hepatic toxicity
3. Consult SmPC for more detailed information on potential drug interactions

Dosing in under 18 years is outside of license but see TangoKids trial for clinical trial data.