VABOREM®▼
meropenem/vaborbactam

SUSPECTED CPE-KPC? THINK VABOREM®

VABOREM®▼ is a combination of meropenem, (a well-known carbapenem), and vaborbactam, (a first-in-class, boron-based, β-lactamase inhibitor). Vaborbactam inhibits KPC, which is one of the carbapenemases responsible for CPE.[1,2,3]

Monotherapy with VABOREM® for CRE infections is associated with increased clinical cure compared with BAT.[3]

BAT, best available therapy; CPE-KPC, carbapenemase producing *Enterobacteriaceae - Klebsiella pneumoniae* carbapenemase; CPE, carbapenemase producing *Enterobacteriaceae.* CRE, carbapenem-resistant *Enterobacteriaceae*

Please note that the term CPE is used throughout this piece, however, when discussing TANGO II the term CRE is used since patients were enrolled on the basis of carbapenem resistance of the baseline pathogen, and not specifically on carbapenemase production. Out of 47 patients in the mCRE-MITT group, 30 had KPC-producing *Klebsiella pneumoniae* at baseline.[3]

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance Website: www.hpra.ie. Adverse events should also be reported to A. Menarini Pharmaceuticals Ireland Ltd. Phone no: 01 284 6744.

A. MENARINI PHARMACEUTICALS IRELAND LTD
Healthcare for Life

When should VABOREM® be used?

VABOREM® is an important treatment option for **CPE-KPC in adults for cUTI** including pyelonephritis; **cIAI; HAP** including **VAP; bacteraemia** that occurs in association with, or is suspected to be associated with any of the infections listed. Also for infections due to **aerobic Gram-negative organisms** in adults with limited treatment options (only after consultation with a physician with appropriate experience in management of infectious diseases). Consideration should be given to official guidance on the appropriate use of antibacterial agents.[1]

Consider VABOREM® when:

✓ Confirmed CPE-KPC[4]

- Confirmed by diagnostic testing, including carbapenemase production and *in vitro* susceptibility testing

✓ Suspected CPE-KPC[4,5,6]

Consider:

- Clinical features of infection and known KPC colonisation
- Previous hospitalisation and prior antibiotic use
- Previous travel to endemic areas
- Local KPC outbreak

Indications: Licensed for use in adults for cUTI including pyelonephritis; cIAI; HAP including VAP; bacteraemia that occurs in association with, or is suspected to be associated with any of the infections listed. Also for infections due to aerobic Gram-negative organisms in adults with limited treatment options (only after consultation with a physician with appropriate experience in management of infectious diseases). Consideration should be given to official guidance on the appropriate use of antibacterial agents.[1]

Limitations of the clinical data: Clinical efficacy for indications is based on experience with meropenem alone, pharmacokinetic-pharmacodynamic analyses of meropenem-vaborbactam, and/or on small randomised controlled trials. [Refer to VABOREM® SPC (2020) section 4.4].

cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; CPE-KPC, carbapenemase producing *Enterobacteriaceae* - *Klebsiella pneumoniae* carbapenemase; VAP, ventilator-associated pneumonia.

Safety and tolerability[1]

Most common side effects

[observed during Phase 3 trials]

- Headache (8.1%)
- Diarrhoea (4.7%)
- Infusion site phlebitis (2.2%)
- Nausea (2.2%)

Contraindications

- Hypersensitivity to any component, or to any carbapenem antibacterial agent
- Severe hypersensitivity to any other type of ß-lactam antibacterial

Interactions

Oral anticoagulants: increases in anticoagulant effects of oral anticoagulants, including warfarin, have been reported in patients receiving antibiotics. [Refer to VABOREM® SPC (2020) section 4.5].

Caution in patients also receiving medicines with a **narrow therapeutic window** that are also metabolised: **predominantly** by CYP450 enzymes (e.g. tacrolimus, everolimus, ciclosporin, lovastatin, midazolam, sildenafil, warfarin)

- by CYP2D6 enzymes (e.g. dextromethorphan, desipramine, venlafaxine, metoprolol)

For further information on side effects, contraindications, interactions and warnings and precautions, please consult the Vaborem SmPC (October 2020).

Warnings and precautions

Hypersensitivity reactions

Serious hypersensitivity reactions (including severe cutaneous adverse reactions) have been reported in patients receiving meropenem. If these occur discontinue immediately and consider alternative treatment.

Seizures

- Seizures have been reported with meropenem
- Patients with known seizure disorders should continue anticonvulsant therapy
- Patients who develop focal tremors, myoclonus, or seizures should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted
- Carbapenems including meropenem may reduce plasma levels of valproic acid to concentrations below therapeutic range increasing risk of breakthrough seizures

Hepatic function monitoring

- Monitor hepatic function closely due to risk of toxicity (hepatic dysfunction with cholestasis and cytolysis)

Clostridium difficile-associated diarrhoea

If reported, discontinuation of VABOREM® and administration of specific treatment for *Clostridium difficile* should be considered. [Refer to VABOREM® SPC (2020)]

Antiglobulin test (Coombs test) seroconversion

A positive direct or indirect Coombs test may develop during treatment with meropenem/vaborbactam as seen with meropenem [Refer to VABOREM® SPC (2020) section 4.8]

Prescribing information

Abbreviated Prescribing Information: Vaborem®▼ 1g/1g powder for concentrate for solution for infusion. (meropenem/vaborbactam) Please consult the Summary of Product Characteristics (SmPC) for full prescribing information. **Presentation:** Powder for concentrate for solution for infusion. **Use:** Adults: complicated urinary tract infection (cUTI), including pyelonephritis; complicated intra-abdominal infection (cIAI); hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP). Patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above. Treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options. **Dosage and administration:** Dose: patients with creatinine clearance ≥40ml/min, 2g/2g infused intravenously over 3 hours every 8 hours. 1g/1g infused intravenously over 3 hours every 8 hours recommended when creatinine clearance is between 20 and 39 ml/min, and every 12 hours when creatinine clearance is between 10 to 19 ml/min. When creatinine clearance is less than 10 ml/min 0.5g /0.5g should be infused intravenously over 3 hours every 12 hours. No dose adjustment for age is required, nor for hepatic impairment. Duration of treatment: *5 to 10 days* (up to 14 days) for patients with cUTI, including pyelonephritis, and cIAI. *7 to 14 days* for HAP, including VAP. *Duration variable, in accordance with the site of infection:* bacteraemia, and infections due to aerobic Gram-negative organisms in patients with limited treatment options. **Contra-indications:** Hypersensitivity to any active constituent or excipient, or to any carbapenem antibacterial agent. History of severe hypersensitivity to any other type of beta-lactam antibacterial agent. **Warnings and Precautions:** Serious and occasionally fatal hypersensitivity reactions have been reported with meropenem and/or meropenem/vaborbactam. Severe subcutaneous adverse reactions have been reported with meropenem. Seizures have been reported with meropenem. Monitor hepatic function due to the risk of hepatic toxicity. A positive direct or indirect Coombs test may develop during treatment with meropenem/vaborbactam as seen with meropenem. The use of meropenem/vaborbactam may result in the overgrowth of non-susceptible organisms. *Clostridium difficile*-associated diarrhoea has been reported with meropenem/vaborbactam. Concomitant use with valproic acid/sodium valproate/valpromide as carbapenems may reduce plasma levels of valproic acid to concentrations below the therapeutic range. Use of Vaborem in cIAI, HAP, including VAP is based on experience with meropenem alone and pharmacokinetic-pharmcodynamic analysis for meropenem-vaborbactam. Use of Vaborem in patients with limited treatment options is based on pharmacokinetic-pharmcodynamic analysis for meropenem-vaborbactam and on limited data from a randomised clinical trial. The inhibitory spectrum of Vaborem includes class A carbapenemases (such as KPC) and class C carbapenemases. Vaborem does not inhibit class D carbapenemase such as OXA-48 or class B metallo-β-lactamases such as NDM and VIM. Contains 250mg of sodium per vial; equivalent to 12.5% of the WHO recommended maximum daily intake of 2g of sodium for an adult. **Interactions:** Products with a narrow therapeutic window that are predominantly metabolised by CYP450 enzymes (e.g. tacrolimus, everolimus, cyclosporine, lovastatin, midazolam, sildenafil, warfarin). Products with a narrow therapeutic index metabolised by CYP2D6 (e.g. dextromethorphan, desipramine, venlafaxine, metoprolol). Probenecid, valproic acid, oral anticoagulation agents. **Pregnancy and lactation:** Avoid during pregnancy. Discontinue breastfeeding prior to initiating therapy. **Side-effects:** Most common adverse reactions in Phase 3 trials: headache, diarrhoea, infusion site phlebitis and nausea. Severe and/or serious adverse effects occurred in 0.9% patients (2 infusion-related reactions and one increase of alkaline phosphatase). Adverse reactions with meropenem alone and/or in Phase 3 trials with Vaborem: Common: thrombocythaemia, hypokalaemia, hypoglycaemia, headache, hypotension, diarrhoea, nausea, vomiting, increased ALT, increased AST, increased blood alkaline phosphatase, increased blood lactate dehydrogenase, infusion site phlebitis, pyrexia. Uncommon: *Clostridium difficile* colitis, vulvovaginal candidiasis, oral candidiasis, leucopenia, neutropenia, eosinophilia, thrombocytopenia, anaphylactic reaction, hypersensitivity, decreased appetite, hyperkalaemia, hyperglycaemia, insomnia, hallucination, tremor, lethargy, dizziness, paraesthesia, phlebitis, vascular pain, bronchospasm, abdominal distension, abdominal pain, increased blood bilirubin, pruritus, rash, urticaria, renal impairment, incontinence, increased blood creatinine, increased blood urea, chest discomfort, infusion site reaction, infusion site erythema, injection site phlebitis, infusion site thrombosis, pain, increased blood creatine phosphokinase, infusion related reaction. Rare: convulsions. Unknown frequency: agranulocytosis, haemolytic anaemia, angioedema, delirium, severe cutaneous adverse reactions (such as toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, DRESS syndrome, acute generalised exanthematous pustulosis), direct and indirect Coombs test positive. **Pack size:** Packs of 6 vials **Legal category:** POM. **Marketing Authorisation Holder:** Menarini International Operations Luxembourg S.A. **Marketing Authorisation number:** EU/1/18/1334/001. **Marketed by:** A. Menarini Pharmaceuticals Ireland Ltd., Castlecourt, Monkstown Farm, Monkstown, Glenageary, Co. Dublin A96 T924. Further information is available on request to A. Menarini Pharmaceuticals Ireland Ltd. or may be found in the SPC. **Last updated:** October 2020.

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1. VABOREM® Summary of Product Characteristics (October 2020). **2.** Petty, L.A. et al. (2018). Overview of meropenem-vaborbactam and newer antimicrobial agents for the treatment of carbapenem-resistant Enterobacteriaceae. Infection and Drug Resistance, 11, pp.1461-1472. **3.** Wunderink, R.G et al. (2018). 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, 7(4), pp.439-455. **4.** A HSE Guide to Treatment of Infection with Carbapenem Resistant Organisms - April 2019 **5.** Magiorakos et al. Antimicrobial Resistance and Infection Control (2017) 6:113 **6.** European Centre for Disease Prevention and Control. Risk assessment on the spread of carbapenemase-producing Enterobacteriaceae (CPE) through patient transfer between healthcare facilities, with special emphasis on cross-border transfer. Stockholm: ECDC; 2011.

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