Summary Report of Benefit-Risk Assessment

VABOREM POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION 1G/1G

NEW DRUG APPLICATION

Active Ingredient(s)	Meropenem/vaborbactam
Product Registrant	A. MENARINI SINGAPORE PTE. LTD.
Product Registration Number	SIN17224P
Application Route	Abridged evaluation
Date of Approval	25 April 2025

Table of Contents

A INTRODUCTION

Vaborem is indicated for the treatment of the following infections in 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.

The active substance, meropenem-vaborbactam, is a beta-lactam/beta-lactamase inhibitor combination that exhibits a dual mechanism of action, combining the antimicrobial activity of meropenem with the beta-lactamase inhibitory effects of vaborbactam. Meropenem exerts bactericidal activity by inhibiting peptidoglycan cell wall synthesis through binding to and inhibiting the activity of essential penicillin-binding proteins. Vaborbactam is an inhibitor of class A and class C serine beta-lactamases, including *Klebsiella pneumoniae* carbapenemase (KPC), and acts by forming a covalent adduct with beta-lactamases, rendering meropenem stable to beta-lactamase-mediated hydrolysis. Vaborbactam does not inhibit class B enzymes (metallo-β-lactamases) or class D carbapenemases.

Vaborem is available as powder for concentrate for solution for infusion in a single-dose vial containing 1g of meropenem and 1g of vaborbactam. Other ingredient in the vial is sodium carbonate.

B ASSESSMENT OF PRODUCT QUALITY

The drug substances, meropenem and vaborbactam, as well as the drug product, Vaborem powder for concentrate for solution for infusion, are manufactured at ACS Dobfar S.P.A, Tribiano, Italy.

Drug substance: Meropenem

The manufacturer has been issued a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) which was submitted to support the application. The description of the manufacturing process steps and in-process controls, control of materials and critical steps, intermediates, process validation, manufacturing process development and characterisation are covered by the CEP.

The drug substance specification is as stated in the CEP and consistent with the current version of the Ph. Eur. monograph for meropenem trihydrate.

The proposed re-test period and packaging material are supported by the CEP. The packaging is sterile bottle-shape polyethylene bag in a sterile polyethylene bag, placed in a sterile four-layer bag. The drug substance is approved for storage at 25°C with a re-test period of 2 years.

Drug substance: Vaborbactam

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in manufacturing process.

The drug substance specifications were established in accordance with ICH Q6A guideline, and the impurity limits have been appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The packaging is sterile bottle-shape low-density polyethylene (LDPE) bag in a high-density polyethylene (HDPE) bag, placed in a four-foil (low-density polyethylene, nylon, aluminium and polyester) bag. The stability data presented was adequate to support the storage of the drug substance at 25°C with a re-test period of 60 months.

Drug product:

The manufacturing process utilises aseptic processing.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with ICH Q6A guideline and impurity limits were adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The container closure system is 50ml Type 1 glass vial sealed with a bromobutyl rubber stopper and capped with an aluminium seal. The stability data submitted was adequate to support the approved shelf-life of 48 months when stored at or below 30°C. The in-use period after reconstitution and dilution is up to 4 hours at 25°C or within 22 hours at 2 – 8°C.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of meropenem-vaborbactam in the treatment of cUTI/AP, cIAI, HABP/VABP and bacteraemia was based on one pivotal Phase III study, Study 505, referred to as the TANGO I study. The application was further supported by one supportive Phase III study, Study 506, referred to as the TANGO II study.

Study 505 (TANGO I) was a multicentre, double-blind, randomised, non-inferiority study of meropenem-vaborbactam compared with piperacillin/tazobactam in patients with complicated urinary tract infections (cUTI) or acute pyelonephritis (AP) requiring hospitalisation and intravenous antibiotic treatment. The study enrolled patients with clinical severity necessitating at least 5 days of intravenous (IV) therapy, including those with structural urinary abnormalities, concurrent bacteraemia, or significant comorbidities.

Patients in the study were randomised in a 1:1 ratio to receive either meropenem 2g-vaborbactam 2g intravenously as a 3-hour infusion every 8 hours or piperacillin/tazobactam 4.5g intravenously as a 30-minute infusion every 8 hours for a minimum of 5 days. After a minimum of 15 doses of IV therapy, patients could be switched to oral levofloxacin 500mg once daily to complete a total treatment course of 10 days (or up to 14 days if clinically indicated in patients with concurrent bacteraemia). The active comparator piperacillin/tazobactam is a combination beta-lactam/beta-lactamase inhibitor with established efficacy against gram-negative pathogens causing cUTI/AP and similar pharmacodynamic properties to meropenem-vaborbactam. The use of piperacillin/tazobactam as an active comparator was considered acceptable.

The study employed dual primary efficacy endpoints in line with international regulatory requirements, comprising overall success at end of intravenous treatment (EOIVT) in the microbiological modified intent-to-treat (m-MITT) population and eradication rate at test of cure (TOC) in both the m-MITT and microbiologically evaluable (ME) populations. Overall success was defined as a composite of clinical outcome (cure or improvement) and microbiological outcome (eradication with $<10^4$ colony-forming units [CFU]/mL of urine). Eradication was defined as reduction of baseline bacterial pathogens to $<10^3$ CFU/mL of urine.

The study employed a pre-specified non-inferiority margin of 15% for the primary efficacy endpoint, which was wider than the 10% margin recommended in the regulatory guidelines. Nevertheless, the pre-defined margin was considered clinically acceptable for cUTI infections as it balances effective treatment outcomes against the potential benefits of activity against resistant pathogens. Furthermore, the more stringent margin of 10% was met for the primary outcome. A hierarchical testing procedure was applied whereby superiority would be examined if non-inferiority was demonstrated, which appropriately controlled for Type I error whilst allowing for sequential non-inferiority and superiority testing.

Secondary efficacy endpoints included overall success rates at both EOIVT and TOC visits, cure rates at multiple time points (Day 3, EOIVT, end of treatment, TOC, and late follow-up), and eradication rates at the same time points using both $<10^4$ CFU/mL and $<10^3$ CFU/mL criteria.

A total of 550 patients were randomised in the study and 545 patients received at least one dose of study drug (MITT population): 272 patients in the meropenem-vaborbactam group and 273 patients in the piperacillin/tazobactam group. The median age was 58.0 years (range 18 to 92 years) in the meropenem-vaborbactam group and 57.0 years (range 18 to 94 years) in the piperacillin/tazobactam group. The study population was predominantly white (92.8%) and female (66.2%). Overall, 60.9% in the meropenem-vaborbactam group and 50.5% in the piperacillin/tazobactam group switched to oral step-down therapy. Mean duration of IV and oral therapy was approximately 10 days in both groups (10.1 days and 9.9 days, respectively).

The majority of patients had *Escherichia coli* (64.7%) or *Klebsiella pneumoniae* (15.5%) as baseline urinary pathogens, with other organisms including *Enterococcus faecalis* (7.2%) and *Pseudomonas aeruginosa* (4.0%). Baseline resistance patterns varied by organism: *K. pneumoniae* showed 33-50% resistance to piperacillin/tazobactam, while *P. aeruginosa* exhibited 25-60% resistance to piperacillin/tazobactam and 40-50% resistance to meropenem.

The study met both primary efficacy endpoints, demonstrating non-inferiority of meropenem-vaborbactam to piperacillin/tazobactam. For the primary endpoint of overall success at end of intravenous treatment in the m-MITT population, meropenem-vaborbactam achieved a 98.4% success rate compared to 94.0% for piperacillin/tazobactam, with a treatment difference of

4.5% (95% CI: 0.7%, 9.1%). Meropenem-vaborbactam was both noninferior (lower CI bound >-15% noninferiority margin) and superior (lower CI bound >0%) to piperacillin/tazobactam. The results also exceeded a more conservative noninferiority margin of -10%. As the lower limit also exceeded 0%, statistical superiority was demonstrated. For eradication rate at test of cure, meropenem-vaborbactam showed higher rates compared to piperacillin/tazobactam in both the m-MITT (66.7% vs 57.7%) and ME (66.3% vs 60.4%) populations, with treatment differences of 9.0% (95% CI: -0.9%, 18.7%) and 5.9% (95% CI: -4.2%, 16.0%), respectively. Both confidence intervals exceeded the prespecified -15% non-inferiority margin as well as the more conservative -10% non-inferiority margin, confirming non-inferiority. The results remained consistent across infection subtypes, including acute pyelonephritis and complicated urinary tract infections with removable or nonremovable sources of infection, and were robust when analysed in the microbiologically evaluable population.

The secondary efficacy endpoints consistently demonstrated numerical advantages for meropenem-vaborbactam compared with piperacillin/tazobactam. Overall success rates at TOC were 74.5% vs 70.3% (difference: 4.1%, 95% CI: -4.9%, 13.2%). Cure rates across all time points from Day 3 through late follow-up showed consistent numerical benefit for meropenem-vaborbactam, with differences ranging from 1.9% to 7.9%. Eradication rates by both $<10^4$ CFU/mL and $<10^3$ CFU/mL criteria followed similar patterns, with meropenem-vaborbactam achieving higher rates at test of cure (68.8% vs 62.1% by $<10^4$ CFU/mL criteria; 66.7% vs 57.7% by $<10^3$ CFU/mL criteria) and late follow-up (68.8% vs 56.6% by $<10^4$ CFU/mL criteria; 67.2% vs 53.8% by $<10^3$ CFU/mL criteria).

Summary of key efficacy results (Study 505)

	Meropenem-Vaborbactam (N=192) N (%)	Piperacillin/ Tazobactam (N=182) N (%)	Treatment Difference (95% CI)
Primary Endpoints			
Overall Success at EOIVT (m-MITT)[1]	189 (98.4%)	171 (94.0%)	4.5% (0.7%, 9.1%)
Eradication at TOC (m-MITT)[2]	128 (66.7%)	105 (57.7%)	9.0% (-0.9%, 18.7%)
Eradication at TOC (ME)[2]	118/178 (66.3%)	102/169 (60.4%)	5.9% (-4.2%, 16.0%)
Secondary Endpoints			
Overall Success at TOC (m-MITT)	143 (74.5%)	128 (70.3%)	4.1% (-4.9%, 13.2%)
Cure Rate at Day 3 (m-MITT)	186 (96.9%)	171 (94.0%)	2.9% (-1.4%, 7.8%)
Cure Rate at EOIVT (m-MITT)	156 (81.3%)	144 (79.1%)	2.8% (-0.7%, 7.1%)
Cure Rate at EOT (m-MITT)	179 (93.2%)	167 (91.8%)	1.9% (-2.9%, 7.0%)
Cure Rate at TOC (m-MITT)	174 (90.6%)	157 (86.3%)	4.4% (-2.2%, 11.1%)
Cure Rate at LFU (m-MITT)	166 (86.5%)	143 (78.6%)	7.9% (0.2%, 15.7%)
Eradication at TOC (m-MITT)[1]	132 (68.8%)	113 (62.1%)	6.7% (-3.0%, 16.2%)
Eradication at LFU (m-MITT)[1]	132 (68.8%)	103 (56.6%)	12.2% (2.3%, 21.8%)
Eradication at LFU (m-MITT)[2]	129 (67.2%)	98 (53.8%)	13.3% (3.4%, 23.0%)

m-MITT = microbiological Modified Intent-to-Treat population (N=192 meropenem-vaborbactam, N=182 piperacillin/tazobactam)
ME = Microbiologically Evaluable population (N=178 meropenem-vaborbactam, N=169 piperacillin/tazobactam)
EOIVT = End of Intravenous Treatment (i.e., on the last day of IV therapy); TOC = Test of Cure (i.e., EOT + 7 days); EOT = End of Treatment (i.e., on the last day of total therapy); LFU = Late Follow-up (i.e., EOT + 14 days)
[1] $<10^4$ CFU/mL criteria; [2] $<10^3$ CFU/mL criteria

Study 506 (TANGO II) was a multicentre, open-label, randomised study of meropenem-vaborbactam compared with investigator-assigned best available therapy (BAT) in patients with severe gram-negative infections suspected or known to be caused by carbapenem-resistant Enterobacteriaceae (CRE). Patients included those with cUTI/AP, complicated intra-abdominal infections, hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP), and bacteraemia caused by pathogens with confirmed or suspected carbapenem resistance mechanisms, including KPC-producing organisms. The open-label

study design, although subject to potential biases, was necessary to allow physicians to customise treatment combinations for each patient given the limited therapeutic options and varying resistance patterns in CRE infections. The study was prematurely terminated on the Data Safety Monitoring Board (DSMB) advice due to an unfavourable interim benefit-risk assessment of BAT.

Patients in the study were randomised in a 2:1 ratio to receive either meropenem 2g-vaborbactam 2g intravenously as a 3-hour infusion every 8 hours or BAT for 7 to 14 days. BAT included carbapenem (meropenem, ertapenem, or imipenem), tigecycline, colistin, aminoglycosides (amikacin, tobramycin, or gentamicin), polymyxin B, and ceftazidime-avibactam, administered either in combination or alone, as determined by the investigator before randomisation. BAT was selected as the comparator due to the absence of a standard treatment for CRE infections, with these agents representing established therapeutic options for carbapenem-resistant infections. The use of these agents as active comparators was appropriate given the limited treatment alternatives available for this patient population.

The efficacy endpoints included clinical cure rates at end of treatment (EOT) and TOC, microbiological eradication rates using both $<10^4$ CFU/mL and $<10^3$ CFU/mL criteria, overall success rates (composite of clinical cure and microbiological eradication), and all-cause mortality at Day 28. These endpoints were assessed across all infection types and specifically within subgroups for each infection site. This study was designed as a descriptive study with no formal hypothesis testing or comparative statistical analyses planned.

When the study was closed on DSMB's advice, a total of 77 patients were randomised in the study and 75 patients received at least one dose of study drug: 50 patients in the meropenem-vaborbactam group and 25 patients in the BAT group. The mean age was 63.6 years (range 29 to 88 years) in the meropenem-vaborbactam group and 63.2 years (range 33 to 83 years) in the BAT group. The study population was predominantly white (86.0% in the meropenem-vaborbactam group and 88.0% in the BAT group) with equal gender distribution in the meropenem-vaborbactam group (50.0% male, 50.0% female). Most patients in the BAT group received combination antibiotic therapy (60.0%), with carbapenems being the most frequent antibiotics used (44.0%). In the cUTI/AP subgroup, *K. pneumoniae* was the most common pathogen and represented 93.8% of CRE recovered in urine, with 75.0% of cUTI/AP patients in the meropenem-vaborbactam group having KPC-producing isolates.

In the overall microbiological population (m-MITT) population, all-cause mortality at Day 28 was 14.3% with meropenem-vaborbactam vs 26.3% with BAT. Clinical cure rates were 68.6% vs 36.8% at EOT and 60.0% vs 31.6% at TOC. In the confirmed CRE population (mCRE-MITT), all-cause mortality was 15.6% vs 33.3%, with clinical cure rates of 65.6% vs 33.3% at EOT and 59.4% vs 26.7% at TOC for meropenem-vaborbactam and BAT, respectively. Subgroup analyses by infection type showed variable results across multiple endpoints, however, interpretation was limited by small sample sizes (cUTI/AP n=16, bacteraemia n=22, HABP/VABP n=5, cIAI n=4).

Summary of key efficacy results (Study 506)

	m-MITT population		**mCRE-MITT population**	
	Meropenem-Vaborbactam (N=35)	**Best Available Therapy (N=19)**	**Meropenem-Vaborbactam (N=32)**	**Best Available Therapy (N=15)**
Overall Population				
Clinical Cure at EOT	24/35 (68.6%)	7/19 (36.8%)	21/32 (65.6%)	5/15 (33.3%)
Clinical Cure at TOC	21/35 (60.0%)	6/19 (31.6%)	19/32 (59.4%)	4/15 (26.7%)

Eradication at EOT	23/35 (65.7%)	8/19 (42.1%)	21/32 (65.6%)	6/15 (40.0%)
Eradication at TOC	17/35 (48.6%)	7/19 (36.8%)	17/32 (53.1%)	5/15 (33.3%)
All-cause Mortality at Day 28	5/35 (14.3%)	5/19 (26.3%)	5/32 (15.6%)	5/15 (33.3%)
cUTI/AP Subgroup				
Overall Success at EOT	10/13 (76.9%)	4/8 (50.0%)	9/12 (75.0%)	2/4 (50.0%)
Overall Success at TOC	4/13 (30.8%)	4/8 (50.0%)	4/12 (33.3%)	2/4 (50.0%)
Clinical Cure at EOT	10/13 (76.9%)	4/8 (50.0%)	9/12 (75.0%)	2/4 (50.0%)
Clinical Cure at TOC	6/13 (46.2%)	4/8 (50.0%)	5/12 (41.7%)	2/4 (50.0%)
Eradication at EOT	9/13 (69.2%)	3/8 (37.5%)	8/12 (66.7%)	2/4 (50.0%)
Eradication at TOC	3/13 (23.1%)	2/8 (25.0%)	3/12 (25.0%)	2/4 (50.0%)
All-cause Mortality at Day 28	1/13 (7.7%)	0/8 (0.0%)	1/12 (8.3%)	0/4 (0.0%)
Bacteraemia Subgroup				
Overall Success at EOT	8/15 (53.3%)	3/8 (37.5%)	7/14 (50.0%)	3/8 (37.5%)
Overall Success at TOC	8/15 (53.3%)	2/8 (25.0%)	7/14 (50.0%)	2/8 (25.0%)
Clinical Cure at EOT	8/15 (53.3%)	3/8 (37.5%)	7/14 (50.0%)	3/8 (37.5%)
Clinical Cure at TOC	9/15 (60.0%)	2/8 (25.0%)	8/14 (57.1%)	2/8 (25.0%)
All-cause Mortality at Day 28	4/15 (26.7%)	3/8 (37.5%)	4/14 (28.6%)	3/8 (37.5%)
HABP/VABP Subgroup				
Clinical Cure at EOT	4/5 (80.0%)	0/1 (0.0%)	3/4 (75.0%)	0/1 (0.0%)
Clinical Cure at TOC	4/5 (80.0%)	0/1 (0.0%)	4/4 (100.0%)	0/1 (0.0%)
All-cause Mortality at Day 28	0/5 (0.0%)	1/1 (100.0%)	0/4 (0.0%)	1/1 (100.0%)
cIAI Subgroup				
Clinical Cure at EOT and TOC	2/2 (100.0%)	0/2 (0.0%)	2/2 (100.0%)	0/2 (0.0%)
All-cause Mortality at Day 28	0/2 (0.0%)	1/2 (50.0%)	0/2 (0.0%)	1/2 (50.0%)

m-MITT = microbiological Modified Intent-to-Treat population (N=35 meropenem-vaborbactam, N=19 BAT)
mCRE-MITT = microbiological Carbapenem-resistant Enterobacteriaceae Modified Intent-to-Treat population (N=32 meropenem-vaborbactam, N=15 BAT)
EOT = End of Treatment
TOC = Test of Cure

Study 506 had significant limitations that did not allow meaningful interpretation of the study results. The study was designed as a descriptive study with no formal hypothesis testing or comparative statistical analyses. The early termination resulted in very small sample sizes across infection types, with only 4 patients with HABP/VABP and 2 patients with cIAI in the meropenem-vaborbactam group. These limited patient numbers precluded definitive conclusions about efficacy in these specific indications. Given these constraints, the broader indications beyond cUTI sought in the application relied substantially on pharmacokinetic-pharmacodynamic (PK-PD) data and the established efficacy of meropenem monotherapy. For cIAI and HABP/VABP indications, the clinical trends observed in Study 506, while based on small numbers, were supported by favourable PK-PD distribution characteristics that demonstrated adequate tissue penetration, supplemented by meropenem's established efficacy in these infection types. For bacteraemia, the indication was based on clinical data from both studies: Study 505 included 12 patients with concurrent bacteraemia, showing 83.3% overall success, while Study 506 included 14 patients with CRE bacteraemia, showing 50.0% overall success and 28.6% mortality. The pharmacokinetic properties of both compounds in plasma, combined with meropenem's established efficacy in septicaemia, was adequate to lend support for the treatment of bacteraemic infections.

Overall, the pivotal Study 505 met both primary efficacy endpoints, establishing non-inferiority and statistical superiority over piperacillin/tazobactam for cUTI and AP. In addition, the supportive Study 506, while limited by early termination and small sample sizes, provided favourable clinical trends for CRE infections across multiple anatomical sites. For indications with limited direct clinical data, there was reasonable PK-PD evidence demonstrating adequate tissue penetration combined with meropenem's established efficacy profile. The consistent efficacy results across patient subgroups and infection types, together with the appropriate

statistical methodology employed, supported the efficacy of meropenem-vaborbactam for the approved indications.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of meropenem-vaborbactam was based primarily on safety data derived from two Phase III studies (Studies 505 and 506), comprising a total of 620 patients who received at least one dose of study treatment: 322 patients in the meropenem-vaborbactam group and 298 patients in the comparator group. The mean (SD) exposure duration (IV and oral therapy) was 10.0 (2.37) days in the meropenem-vaborbactam group and 9.8 (2.38) days in the comparator group. Analysis of actual IV therapy exposure days demonstrated a mean (SD) of 8.2 (2.81) days in the meropenem-vaborbactam group and 8.1 (2.76) days in the comparator group. The exposure durations were similar between treatment groups, with more than half of the patients in both groups receiving ≥7 days of IV therapy (61.3% in the meropenem-vaborbactam group and 60.9% in the comparator group).

Overview of safety profile (Pooled Phase III data)

AE	Meropenem-vaborbactam (N=322)	Comparators (N=298)
Any AE	148 (46.0%)	120 (40.3%)
Treatment-related AE	53 (16.5%)	46 (15.4%)
SAE	28 (8.7%)	23 (7.7%)
Treatment-related SAE	1 (0.3%)	3 (1.0%)
Discontinuations due to AE	12 (3.7%)	17 (5.7%)
Deaths due to AE	12 (3.7%)	8 (2.7%)
Treatment-related deaths due to AE	0 (0%)	0 (0%)

A total of 46.0% of patients in the meropenem-vaborbactam group and 40.3% in the comparator group experienced at least one adverse event (AE). Drug-related AEs occurred at similar frequencies in the meropenem-vaborbactam group (16.5%) and the comparator group (15.4%). The most frequently reported AEs (≥2% in either group) were headache (8.1% vs 4.0%), diarrhoea (4.7% vs 5.4%), hypokalaemia (2.5% vs 2.0%), anaemia (2.2% vs 2.3%), nausea (2.2% vs 2.0%), infusion site phlebitis (2.2% vs 1.0%), and dyspnoea (0.6% vs 2.0%) for meropenem-vaborbactam and comparator groups, respectively. Headache was the only AE that occurred at a ≥2% higher incidence in the meropenem-vaborbactam group (8.1%) compared to the comparator group (4.0%).

The incidence of serious adverse events (SAEs) was comparable between groups (meropenem-vaborbactam: 8.7%; comparator: 7.7%). The most frequently reported SAEs (>1 patient overall) included sepsis (0.9% vs 1.3%), septic shock (0.6% vs 1.7%), cardiac arrest (0.6% vs 0%), and general physical health deterioration (0.6% vs 0%). Drug-related SAEs were infrequent in both groups, occurring in 0.3% of meropenem-vaborbactam patients compared to 1.0% of comparator patients. One SAE of infusion-related reaction was considered probably related to meropenem-vaborbactam treatment, with the patient recovering within a few hours after study drug discontinuation. In the comparator group, one *Clostridium difficile* colitis, one seizure, and one *Enterococcus faecium* sepsis were deemed related to treatment.

Treatment discontinuation due to AEs occurred at a comparable rate in the meropenem-vaborbactam group (3.7%) compared with the comparator group (5.7%). In the meropenem-vaborbactam group, the most frequently reported AEs leading to discontinuation (>1 patient overall) were cardiac arrest (0.6%) and infusion-related reaction (0.6%).

Deaths occurred in 12 patients (3.7%) in the meropenem-vaborbactam group and 8 patients (2.7%) in the comparator group. The most common fatal events were septic shock (0.3% vs 1.7%), sepsis (0.6% vs 0.3%), cardiac arrest (0.6% vs 0%), and general physical health deterioration (0.6% vs 0%). None of the deaths were attributed to study drug by the investigators. All fatal events were consistent with the severity of the patients' underlying infections or comorbidities, reflecting the seriously ill nature of the study population requiring treatment for severe bacterial infections.

The most frequently reported adverse events of special interest (AESIs) were hypersensitivity reactions (4.0% vs 4.4%) and pseudomembranous colitis/*Clostridium difficile*-associated diarrhoea (CDAD) (0.6% vs 1.0%). Hypersensitivity reactions in the meropenem-vaborbactam group included infusion-related reaction (0.6%), anaphylactic reaction (0.3%), urticaria (0.3%), bronchospasm (0.3%), hypersensitivity (0.3%). Four of the hypersensitivity reactions required discontinuation or interruption of meropenem-vaborbactam treatment. CDAD was reported in 1 patient (0.3%) treated with meropenem-vaborbactam vs 2 patients (0.7%) in the comparator group, while pseudomembranous colitis was reported in 1 patient in each group.

Seizures, a known risk with carbapenem antibiotics, were not reported in any meropenem-vaborbactam-treated patients compared to 2 patients (0.7%) in the comparator group. Both seizure cases in the comparator group were serious adverse events that resolved; one was considered possibly related to piperacillin/tazobactam treatment while the other was considered unrelated to colistin treatment.

Overall, the safety profile of meropenem-vaborbactam was consistent with that of other beta-lactam/beta-lactamase inhibitor combinations, with AEs predominantly comprising headache and infusion site reactions. The observed AEs in the treatment of cUTI, HABP/VABP, cIAI and bacteraemia were manageable and no major safety concerns were raised.

E ASSESSMENT OF BENEFIT-RISK PROFILE

CRE poses a significant challenge to healthcare systems worldwide, with limited treatment options and increasing mortality and morbidity risks for patients with serious bacterial infections. The primary carbapenemases include *K. pneumoniae* carbapenemases (KPC), New Delhi metallo-β-lactamases (NDM), and oxacillinases (e.g., OXA-48). Vaborem is a combination product comprising meropenem and vaborbactam. Meropenem, a broad-spectrum carbapenem antibiotic, demonstrated efficacy against various gram-positive, gram-negative, and anaerobic bacteria; whereas vaborbactam, a novel beta-lactamase inhibitor, was specifically designed to inhibit KPC beta-lactamase and enhance carbapenem efficacy against Enterobacteriaceae.

The pivotal Phase III study (TANGO I) evaluated the clinical efficacy of meropenem-vaborbactam in the treatment of cUTI and AP. The study met both primary efficacy endpoints, showing that meropenem-vaborbactam was both non-inferior and statistically superior to piperacillin/tazobactam. The primary endpoint of overall success at EOIVT demonstrated meropenem-vaborbactam achieving a 98.4% success rate compared to 94.0% for piperacillin/tazobactam, with a treatment difference of 4.5% (95% CI: 0.7%, 9.1%). The primary endpoint of eradication rate at TOC also favoured meropenem-vaborbactam in both the m-MITT (66.7% vs 57.7%) and ME populations (66.3% vs 60.4%), with confidence intervals exceeding both the prespecified -15% and more conservative -10% non-inferiority margins.

Secondary endpoints consistently demonstrated numerical advantages for meropenem-vaborbactam across all time points, with cure rates showing differences ranging from 1.9% to 7.9% and eradication rates following similar patterns.

The supportive Phase III study (TANGO II) evaluated meropenem-vaborbactam against BAT in patients with CRE infections across multiple anatomical sites. The study was prematurely terminated on DSMB advice due to an unfavourable interim benefit-risk assessment of BAT. The results showed numerically higher clinical cure rates for meropenem-vaborbactam compared to BAT in the overall population (68.6% vs 36.8% at EOT), while all-cause mortality rates were numerically lower (14.3% vs 26.3% at Day 28). However, the study had significant limitations including early termination, small sample sizes, and lack of formal statistical testing, which did not allow any meaningful interpretation of these results. The study was designed as a descriptive study with no formal hypothesis testing or comparative statistical analyses planned.

For the indications of cIAI and HABP/VABP, while the clinical data from Study 506 was limited due to small patient numbers, the observed clinical trends were favourable. Supplementary PK-PD data demonstrated adequate tissue penetration and distribution, and further substantiated by meropenem's established efficacy in these infection types. For bacteraemia associated with the approved infection sites, the indication was supported by clinical data from both studies, with Study 505 showing 83.3% overall success in 12 patients with concurrent bacteraemia and Study 506 demonstrating 50.0% overall success with 28.6% mortality in 14 patients with CRE bacteraemia.

The safety profile of meropenem-vaborbactam was comparable to established beta-lactam/beta-lactamase inhibitor combinations and no new safety signals were observed. Treatment-related AEs occurred at similar frequencies between meropenem-vaborbactam (16.5%) and comparators (15.4%), with the most common events being headache (8.1%), diarrhoea (4.7%), and infusion site phlebitis (2.2%). These AEs were consistent with the known safety profile of carbapenem antibiotics and are manageable in the clinical setting. SAEs were infrequent and comparable between groups (8.7% vs 7.7%), with only one drug-related SAE (infusion-related reaction) attributed to meropenem-vaborbactam treatment, and the patient recovered within hours after discontinuation. No seizures were reported in meropenem-vaborbactam-treated patients compared to 2 cases in the comparator group. Treatment discontinuation rates due to AEs were lower with meropenem-vaborbactam (3.7%) compared to comparators (5.7%), and no deaths were attributed to meropenem-vaborbactam treatment by investigators.

Overall, the benefit-risk profile of meropenem-vaborbactam in the treatment of cUTI, HABP/VABP, cIAI and bacteraemia was considered positive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Vaborem for the treatment of cUTI, HABP/VABP, cIAI and bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above was deemed favourable and approval of the product registration was granted on 25 April 2025.

APPROVED PACKAGE INSERT AT REGISTRATION

SINGAPORE PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

Vaborem 1 g/1 g powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains meropenem trihydrate equivalent to 1 g meropenem, and 1 g vaborbactam.

After reconstitution, 1 ml of the solution contains 50 mg meropenem and 50 mg vaborbactam (see section 6.6).

Excipient with known effect:

Each vial contains 10.9 mmol of sodium (approximately 250 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

White to light yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vaborem is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1):

- Complicated urinary tract infection (cUTI), including pyelonephritis
- Complicated intra-abdominal infection (cIAI)
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP).

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Table 1 shows the recommended intravenous dose for patients with a creatinine clearance (CrCl) ≥40 ml/min (see sections 4.4 and 5.1).

Table 1: Recommended intravenous dose for patients with a creatinine clearance (CrCl) ≥40 ml/min[1]

Type of infection	Dose of Vaborem (meropenem/ vaborbactam)[2]	Frequency	Infusion time	Duration of treatment
Complicated UTI (cUTI), including pyelonephritis	2 g/2 g	Every 8 hours	3 hours	5 to 10 days[2]
cIAI	2 g/2 g	Every 8 hours	3 hours	5 to 10 days[2]
Hospital-acquired pneumonia (HAP), including VAP	2 g/2 g	Every 8 hours	3 hours	7 to 14 days
Bacteraemia, in association with, or suspected to be associated with, any of the infections listed above	2 g/2 g	Every 8 hours	3 hours	Duration in accordance with the site of infection

[1] As calculated using the Cockcroft-Gault formula
[2] Treatment may continue up to 14 days

Special populations

Elderly
No dose adjustment based on age is required (see section 5.2).

Renal impairment
Table 2 shows the recommended dose adjustments for patients with a CrCl ≤39 ml/min.

Meropenem and vaborbactam are removed by haemodialysis (see section 5.2). Doses adjusted for renal impairment should be administered after a dialysis session.

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

Hepatic impairment
No dose adjustment is required in patients with hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of meropenem/vaborbactam in children and adolescents younger than 18 years of age have not yet been established. No data are available.

Method of administration

Intravenous use.

Vaborem is administered by intravenous infusion over 3 hours.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Hypersensitivity to any carbapenem antibacterial agent.

Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins, cephalosporins or monobactams).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions have been reported with meropenem and/or meropenem/vaborbactam (see sections 4.3 and 4.8).

Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibacterial agents may also be hypersensitive to meropenem/vaborbactam. Before initiating therapy with Vaborem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.

If a severe allergic reaction occurs, treatment with Vaborem must be discontinued immediately and adequate emergency measures must be initiated. Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM) and acute generalised exanthematous pustulosis (AGEP) have been reported in patients receiving meropenem (see section 4.8). If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and an alternative treatment should be considered.

Seizures

Seizures have been reported during treatment with meropenem (see section 4.8).

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. If necessary, the dose of meropenem/vaborbactam should be adjusted based on renal function (see section 4.2). Alternatively, meropenem/vaborbactam should be discontinued (see section 4.5).

Hepatic function monitoring

Hepatic function should be closely monitored during treatment with meropenem/vaborbactam due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis) (see section 4.8).

Patients with pre-existing liver disorders should have liver function monitored during treatment with meropenem/vaborbactam. There is no dose adjustment necessary (see section 4.2).

Antiglobulin test (Coombs test) seroconversion

A positive direct or indirect Coombs test may develop during treatment with meropenem/vaborbactam as seen with meropenem (see section 4.8).

Clostridium difficile-associated diarrhoea

Clostridium difficile-associated diarrhoea has been reported with meropenem/vaborbactam. The condition can range in severity from mild diarrhoea to fatal colitis and should be considered in patients who present with diarrhoea during or subsequent to the administration of Vaborem (see section 4.8). Discontinuation of therapy with Vaborem and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Concomitant use with valproic acid/sodium valproate/valpromide

Case reports in the literature have shown that co-administration of carbapenems, including meropenem, to patients receiving valproic acid or divalproex sodium may reduce plasma levels of valproic acid to concentrations below the therapeutic range as a result of this interaction, thus increasing the risk of breakthrough seizures. If administration of Vaborem is necessary, supplemental anticonvulsant therapy should be considered (see section 4.5).

Limitations of the clinical data

Complicated intra-abdominal infections
The use of Vaborem to treat patients with complicated intra-abdominal infections is based on experience with meropenem alone and pharmacokinetic-pharmacodynamic analyses of meropenem/vaborbactam.

Hospital-acquired pneumonia, including ventilator-associated pneumonia
The use of Vaborem to treat patients with hospital-acquired pneumonia, including ventilator-associated pneumonia, is based on experience with meropenem alone and pharmacokinetic-pharmacodynamic analyses for meropenem/vaborbactam.

Patients with limited treatment options
The use of Vaborem to treat patients with infections due to bacterial organisms who have limited treatment options is based on pharmacokinetic/pharmacodynamic analyses for meropenem/vaborbactam and on limited data from a randomised clinical study in which 32 patients were treated with Vaborem and 15 patients were treated with best available therapy for infections caused by carbapenem-resistant organisms (see section 5.1). Clinical discretion may be exercised in scenarios where no alternative treatment options are available.

Spectrum of activity of meropenem/vaborbactam

Meropenem does not have activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE) or vancomycin-resistant *Enterococci* (VRE). Alternative or

additional antibacterial agents should be used when these pathogens are known or suspected to be contributing to the infectious process.

The inhibitory spectrum of vaborbactam includes class A carbapenemases (such as KPC) and Class C carbapenemases. Vaborbactam does not inhibit class D carbapenemases such as OXA-48 or class B metallo-β-lactamases such as NDM and VIM (see section 5.1).

Non-susceptible organisms

The use of meropenem/vaborbactam may result in the overgrowth of non-susceptible organisms, which may require interruption of treatment or other appropriate measures.

Controlled sodium diet

Vaborem contains 250 mg of sodium per vial, equivalent to 12,5% of the WHO recommended maximum daily intake of 2 g of sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data suggests a potential for induction of CYP1A2 (meropenem), CYP3A4 (meropenem and vaborbactam) and potentially other PXR regulated enzymes and transporters (meropenem and vaborbactam). When administering Vaborem concomitantly with medicinal products that are predominantly metabolised by CYP1A2 (e.g theophylline), CYP3A4 (e.g alprazolam, midazolam, tacrolimus, sirolimus, cyclosporine, simvastatin, omeprazole, nifedipine, quinidine and ethinylestradiol) and/or CYP2C (e.g. warfarin, phenytoin) and/or transported by P-gp (e.g. dabigatran, digoxin) there could be a potential risk of interaction which may result in decreased plasma concentrations and activity of the co-administered medicinal product. Therefore, patients taking such medicinal products should be monitored for possible clinical signs of altered therapeutic efficacy.
Both meropenem and vaborbactam are substrates of OAT3 and as such, probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem and the same mechanism could apply for vaborbactam. Co-administration of probenecid with Vaborem is not recommended, as it may result in increased plasma concentrations of meropenem and vaborbactam.

Concomitant administration of meropenem and valproic acid has been associated with reductions in valproic acid concentrations with subsequent loss in seizure control. Data from *in vitro* and animal studies suggest that carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA g) back to valproic acid, thus decreasing the serum concentrations of valproic acid. Therefore, supplemental anticonvulsant therapy should be administered when concomitant administration of valproic acid and meropenem/vaborbactam cannot be avoided (see section 4.4).

Oral anticoagulants

Simultaneous administration of antibacterial agents with warfarin may augment its anticoagulant effects. There have been many reports of increases in the anticoagulant effects of orally administered anticoagulants, including warfarin in patients, who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibacterial agent to the increase in international normalised ratio (INR) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of Vaborem with an oral anticoagulant.

Contraceptives

Vaborem may decrease the efficacy of hormonal contraceptive medicinal products containing oestrogen and/or progesterone. Women of childbearing potential should be advised to use alternative effective contraceptive methods during treatment with Vaborem and for a period of 28 days after discontinuation of treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of meropenem/vaborbactam in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Vaborem during pregnancy.

Breast-feeding

Meropenem has been reported to be excreted in human milk. It is unknown whether vaborbactam is excreted in human milk or animal milk. Because a risk to the newborns/infants cannot be excluded, breastfeeding must be discontinued prior to initiating therapy.

Fertility

The effects of meropenem/vaborbactam on fertility in humans have not been studied. Animal studies conducted with meropenem and vaborbactam do not indicate harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Vaborem has moderate influence on the ability to drive and use machines. Seizures have been reported during treatment with meropenem alone, especially in patients treated with anticonvulsants (see section 4.4). Meropenem/vaborbactam may cause headache, paraesthesia, lethargy and dizziness (see section 4.8). Therefore, caution should be exercised when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions that occurred among 322 patients from the pooled Phase 3 studies were headache (8.1%), diarrhoea (4.7%), infusion site phlebitis (2.2%) and nausea (2.2%).

Severe adverse reactions were observed in two patients (0.6 %), one infusion related reaction and one blood alkaline phosphatase increased respectively. In one additional patient, a serious adverse reaction of infusion related reaction was reported (0.3%).

Tabulated list of adverse reactions

The following adverse reactions have been reported with meropenem alone and/or identified during the Phase 3 studies with Vaborem. Adverse reactions are classified according to frequency and System Organ Class. Adverse reactions listed in the table with a frequency of "unknown" were not observed in patients participating in studies with Vaborem or meropenem but have been reported in the post-marketing setting for meropenem alone.

Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); unknown (cannot be estimated from the available data). Within each System Organ Class, undesirable effects are presented in order of decreasing seriousness.

Table 3: Frequency of adverse reactions by system organ class

System organ class	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Unknown** (cannot be estimated from the available data)
Infections and infestations		*Clostridium difficile* colitis Vulvovaginal candidiasis Oral candidiasis		
Blood and lymphatic system disorders	Thrombocythaemia	Leucopenia Neutropenia Eosinophilia Thrombocytopenia		Agranulocytosis Haemolytic anaemia
Immune system disorders		Anaphylactic reaction Hypersensitivity		Angioedema
Metabolism and nutrition disorders	Hypokalaemia Hypoglycaemia	Decreased appetite Hyperkalaemia Hyperglycaemia		
Psychiatric disorders		Insomnia Hallucination		Delirium
Nervous system disorders	Headache	Tremor Lethargy Dizziness Paraesthesia	Convulsions	
Vascular disorders	Hypotension	Phlebitis Vascular pain		
Respiratory, thoracic and mediastinal disorders		Bronchospasm		
Gastrointestinal disorders	Diarrhoea Nausea Vomiting	Abdominal distension Abdominal pain		

System organ class	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Unknown** (cannot be estimated from the available data)
Hepatobiliary disorders	Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphatase increased Blood lactate dehydrogenase increased	Blood bilirubin increased		
Skin and subcutaneous disorders		Pruritus Rash Urticaria		Severe cutaneous adverse reactions (SCAR), such as Toxic epidermal necrolysis (TEN) Stevens Johnson syndrome (SJS) Erythema multiforme (EM) Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) Acute generalised exanthematous pustulosis (AGEP) (see section 4.4)
Renal and urinary disorders		Renal impairment Incontinence Blood creatinine increased Blood urea increased		
General disorders and administration site conditions	Infusion site phlebitis Pyrexia	Chest discomfort Infusion site reaction		

System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Unknown (cannot be estimated from the available data)
		Infusion site erythema Injection site phlebitis Infusion site thrombosis Pain		
Investigations		Blood creatine phosphokinase increased		Direct and indirect Coombs test positive
Injury, poisoning and procedural complications		Infusion related reaction		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

There is no experience with overdose of Vaborem.

Limited post-marketing experience with meropenem alone indicates that if adverse reactions occur following overdose, they are consistent with the adverse reaction profile described in section 4.8, are generally mild in severity and resolve on withdrawal or dose reduction.

In the event of overdose, discontinue Vaborem and institute general supportive treatment. In individuals with normal renal function, rapid renal elimination will occur.

Meropenem and vaborbactam can be removed by haemodialysis. In subjects with end stage renal disease (ESRD) administered 1 g meropenem and 1 g vaborbactam, the mean total recovery in dialysate following a haemodialysis session was 38% and 53% for meropenem and vaborbactam, respectively.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, carbapenems, ATC code: J01DH52

Mechanism of action

Meropenem exerts bactericidal activity by inhibiting peptidoglycan cell wall synthesis as a result of binding to and inhibition of activity of essential penicillin-binding proteins (PBPs).

Vaborbactam is a non-beta-lactam inhibitor of class A and class C serine beta-lactamases, including *Klebsiella pneumoniae* carbapenemase, KPC. It acts by forming a covalent adduct with beta-lactamases and is stable to beta-lactamase-mediated hydrolysis. Vaborbactam does not inhibit class B enzymes (metallo-β-lactamases) or class D carbapenemases. Vaborbactam has no antibacterial activity.

Resistance

Mechanisms of resistance in Gram-negative bacteria that are known to affect meropenem/vaborbactam include organisms that produce metallo-β-lactamases or oxacillinases with carbapenemase activity.

Mechanisms of bacterial resistance that could decrease the antibacterial activity of meropenem/vaborbactam include porin mutations affecting outer membrane permeability and overexpression of efflux pumps.

Antibacterial activity in combination with other antibacterial agents

In vitro studies demonstrated no antagonism between meropenem/vaborbactam and levofloxacin, tigecycline, polymyxin, amikacin, vancomycin, azithromycin, daptomycin or linezolid.

Susceptibility testing break points

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST - Breakpoint tables for interpretation of MICs and zone diameters, version 1.0, 2021) are as follows:

	Minimum Inhibitory Concentrations (mg/l)	
Organisms	**Susceptible**	**Resistant**
Enterobacterales	≤8[1]	>8[1]
Pseudomonas aeruginosa	≤8[1]	>8[1]

[1]For susceptibility testing purposes, the concentration of vaborbactam is fixed at 8 mg/l.

Pharmacokinetic/pharmacodynamic relationship

The antimicrobial activity of meropenem has been shown to best correlate with the percent of the dosing interval during which the free meropenem concentrations in plasma exceed the meropenem minimum inhibitory concentration. For vaborbactam, the PK-PD index associated with antimicrobial activity is the ratio of free vaborbactam plasma AUC: meropenem/vaborbactam MIC.

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against the following pathogens that were susceptible to meropenem/vaborbactam *in vitro*.

Complicated urinary-tract infections, including pyelonephritis
Gram-negative micro-organisms:

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Enterobacter cloacae species* complex

Clinical efficacy has not been established against the following pathogens that are relevant to the approved indications although *in vitro* studies suggest that they would be susceptible to meropenem and/or meropenem/vaborbactam in the absence of acquired mechanisms of resistance.

Gram-negative micro-organisms:

- *Citrobacter freundii*
- *Citrobacter koseri*
- *Klebsiella aerogenes*
- *Klebsiella oxytoca*
- *Morganella morganii*
- *Proteus mirabilis*
- *Providencia spp.*
- *Pseudomonas aeruginosa*
- *Serratia marcescens*

Gram-positive micro-organisms:

- *Staphylococcus saprophyticus*
- *Staphylococcus aureus (*methicillin susceptible isolates only)
- *Staphylococcus epidermidis (*methicillin susceptible isolates only)
- *Streptococcus agalactiae*

Anaerobic micro-organisms:

- *Bacteroides fragilis*
- *Bacteroides thetaiotaomicron*
- *Clostridium perfringens*
- *Peptoniphilus asaccharolyticus*
- *Peptostreptococcus species (including P. micros, P anaerobius, P. magnus)*
- *Bacteroides caccae*
- *Prevotella bivia*
- *Prevotella disiens*

5.2 Pharmacokinetic properties

Distribution

The plasma protein binding of meropenem is approximately 2%. The plasma protein binding of vaborbactam is approximately 33%.

The steady-state volumes of distribution of meropenem and vaborbactam in patients were 20.2 L and 18.6 L, respectively, following doses of 2 g meropenem/2 g vaborbactam infused over 3 hours every 8 hours, indicating that both compounds distribute into a volume of distribution consistent with the extracellular fluid compartment.

Both meropenem and vaborbactam penetrate into human bronchial epithelial lining fluid (ELF) with concentrations around 65% and 79% of unbound plasma concentrations of meropenem and vaborbactam, respectively. The concentration time profiles are similar for ELF and plasma.

Biotransformation

Meropenem is mostly eliminated unchanged. About 25% of the administered dose is eliminated as the inactive open ring form.

Vaborbactam does not undergo metabolism.

Elimination

The terminal half-life (t½) is 2.30 hours and 2.25 hours for meropenem and vaborbactam, respectively.

Both meropenem and vaborbactam are primarily excreted via the kidneys. Approximately 40-60% of a meropenem dose is excreted unchanged within 24 - 48 hours with a further 25% recovered as the microbiologically inactive hydrolysis product. The elimination of meropenem by the kidneys resulted in high therapeutic concentrations in urine. The mean renal clearance for meropenem was 7.7 L/h. The mean non-renal clearance for meropenem was 4.8 L/h, which comprises both fecal elimination (~2% of the dose) and degradation due to hydrolysis.

Approximately 75 to 95% of vaborbactam is excreted unchanged in the urine over a 24 - 48 hour period. The elimination of vaborbactam by the kidneys resulted in high concentrations in the urine. The mean renal clearance for vaborbactam was 10.5 L/h.

Linearity/non-linearity

The C_{max} and AUC of meropenem and vaborbactam are linear across the dose range studied (1 g to 2 g for meropenem and 0.25 g to 2 g for vaborbactam) when administered as a single 3-hour intravenous infusion. There is no accumulation of meropenem or vaborbactam following multiple intravenous infusions administered every 8 hours for 7 days in subjects with normal renal function.

Effect of vaborbactam/meropenem on enzymes and transporters

Neither meropenem nor vaborbactam inhibit CYP450 enzymes *in vitro* at pharmacologically relevant concentrations.

Both meropenem and vaborbactam do not inhibit renal or hepatic transporters at pharmacologically relevant concentrations.

Special populations

Renal impairment
Pharmacokinetic studies with meropenem and vaborbactam in patients with renal impairment have shown that the plasma clearance of both meropenem and vaborbactam correlates with creatinine clearance.

Hepatic impairment
As meropenem/vaborbactam does not undergo hepatic metabolism, the systemic clearance of meropenem/vaborbactam is not expected to be affected by hepatic impairment.

Elderly
Pharmacokinetic data from a population pharmacokinetic analysis showed a reduction in plasma clearance of meropenem/vaborbactam that correlates with age-associated reduction in creatinine clearance.

Gender and race
In a population pharmacokinetic analysis there was no effect of gender or race on the pharmacokinetics of meropenem and vaborbactam.

5.3 Preclinical safety data

Meropenem

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, reproduction toxicity or genotoxicity. Carcinogenicity studies have not been conducted with meropenem.

Vaborbactam

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, reproduction toxicity or genotoxicity. Carcinogenicity studies have not been conducted with vaborbactam.

In repeat dose toxicity studies in dogs, minimal hepatic inflammation was observed after 14 days and 28 days of exposure to vaborbactam alone or combined meropenem/vaborbactam.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate

6.2 Incompatibilities

Vaborem is not chemically compatible with glucose-containing solutions. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

The expiry date is stated on the packaging.

After reconstitution

The reconstituted vial should be further diluted immediately.

After dilution

The chemical and physical in-use stability has been demonstrated for up to 4 hours at 25 °C or within 22 hours at 2 – 8 °C.

From a microbiological point of view, the medicinal product should be used immediately upon reconstitution and dilution.

6.4 Special precautions for storage

Store below 30°C.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

50 ml clear glass vial (Type 1) closed with a rubber (bromobutyl) stopper and aluminium overseal with flip-off cap.

The medicinal product is supplied in packs of 6 vials.

6.6 Special precautions for disposal and other handling

Standard aseptic techniques must be used for solution preparation and administration.

The powder for concentrate for solution for infusion must be reconstituted and further diluted prior to use.

Reconstitution

20 ml of sodium chloride 9 mg/ml (0.9%) solution for injection (normal saline) should be withdrawn from a 250 ml infusion bag of sodium chloride 9 mg/ml (0.9%) solution for injection for each vial and reconstituted with the appropriate number of vials of meropenem/vaborbactam for the corresponding Vaborem dosage:

- Reconstitute 2 vials for the Vaborem 2 g/2 g dose
- Reconstitute 1 vial for the Vaborem 1 g/1 g and Vaborem 0.5 g/0.5 g doses

After mixing gently to dissolve, the reconstituted meropenem/vaborbactam solution will have an approximate meropenem concentration of 0.05 g/ml and an approximate vaborbactam concentration of 0.05 g/ml. The final volume is approximately 21.3 ml. The reconstituted solution is not for direct injection. The reconstituted solution must be diluted before intravenous infusion.

Dilution

To prepare the Vaborem 2 g/2 g dose for intravenous infusion: Immediately after reconstitution of two vials, the entire reconstituted vial contents should be withdrawn from each of the two vials and added back into the 250 ml infusion bag of sodium chloride 9 mg/ml (0.9%) solution for injection (normal saline). The final infusion concentration of meropenem and vaborbactam will be about 8 mg/ml each.

To prepare the Vaborem 1 g/1 g dose for intravenous infusion: Immediately after reconstitution of one vial, the entire reconstituted vial contents should be withdrawn from the vial and added back into the 250 ml infusion bag of sodium chloride 9 mg/ml (0.9%) solution for injection (normal saline). The final infusion concentration of meropenem and vaborbactam will be about 4 mg/ml each.

To prepare the Vaborem 0.5 g/0.5 g dose for intravenous infusion: Immediately after reconstitution of one vial,10.5 ml of the reconstituted vial contents should be withdrawn from the vial and added back into the 250 ml infusion bag of sodium chloride 9 mg/ml (0.9%) solution for injection (normal saline). The final infusion concentration of meropenem and vaborbactam will be 2 mg/ml each.

The diluted solution should be inspected visually for particulate matter. The colour of the diluted solution is clear to light yellow.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT REGISTRANT

A. Menarini Singapore Pte. Ltd.
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8. DATE OF REVISION OF THE TEXT

17 April 2025