Date: 30 September 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Vaborem

International non-proprietary name: meropenem trihydrate, vaborbactam
Pharmaceutical form: powder for concentrate for solution for infusion
Dosage strength: 1g/1g
Route(s) of administration: intravenous use
Marketing Authorisation Holder: A. Menarini AG
Marketing Authorisation No.: 67797
Decision and Decision date: approved on 01.07.2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of the SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
AM	Alveolar macrophages
AP	Acute pyelonephritis
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
AUCinf	Area under the plasma concentration-time curve to infinity
BAT	Best available therapy
CEP	Certificate of Suitability of the European Pharmacopoeia
cIAI	Complicated intra-abdominal infections
Cmax	Maximum observed plasma/serum concentration of drug
Cmax,ss	Maximum steady state observed plasma/serum concentration of drug
CRE	Carbapenem-resistant Enterobacteriaceae
cUTI	Complicated urinary tract infection
CYP	Cytochrome P450
DSMB	Data Safety Monitoring Board
eGFR	Estimated glomerular filtration
ELF	Epithelial lining fluid
EMAX	Maximum reduction
ERA	Environmental Risk Assessment
ESRD	End-stage renal disease
GLP	Good Laboratory Practice
HABP	Hospital-acquired bacterial pneumonia
HAP	Hospital-acquired pneumonia
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
KPC	Klebsiella pneumoniae carbapenemase
LC-MS	Liquid chromatography–mass spectrometry
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
mCRE-MITT	Microbiological carbapenem-resistant Enterobacteriaceae modified intention-to-treat
Min	Minimum
m-MITT	Microbiological modified intention-to-treat
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
OAT	Organic anion transporter
PD	Pharmacodynamics
Pgp	P-glycoprotein
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PKPD	Pharmacokinetic/pharmacodynamic
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
ΔΔQTcF	Placebo-corrected, change-from-baseline QTcF
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TID	Three times a day

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TOC	Test of cure
TPA	Federal Act of 15 December 2000 (status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
VABP	Ventilator-associated bacterial pneumonia
VAP	Ventilator-associated pneumonia
Vc	Volume of distribution of the central compartment

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance Status
The applicant requested the status of a new active entity for the active substance vaborbactam in combination with meropenem for the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Vaborem is indicated for the treatment of the following infections in adults (see sections Warnings and precautions and Properties/Effects):
• 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 of being associated with, any of the infections listed above.
Vaborem is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options (see sections Posology, Warnings and precautions and Properties/Effects).
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

2.2.2 Approved Indication

Vaborem is indicated for the treatment of the following infections in adults only if it is established or strongly suspected after microbiological sensitivity testing that the infection is caused by sensitive bacteria (see "Warnings and precautions" and "Properties/Effects"):
- 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 of being associated with, any of the infections listed above.

To prevent rapid development of resistance to Vaborem, Vaborem must not be used for the treatment of such infections unless the antibiotics recommended for empirical initial treatment of these infections are not considered appropriate (see "Warnings and precautions"). Consideration should be given to official guidance on the appropriate use of antibacterial agents.

It is therefore recommended that the decision to prescribe Vaborem and initiation of therapy occur in a hospital setting under the direction of a specialist, e.g. a specialist in infectious diseases.

2.2.3 Requested Dosage

Usual dosage
Table 1 shows the recommended intravenous dose for patients with a creatinine clearance (CrCl) ≥40 ml/min (see sections Warnings and precautions and Properties/Effects).

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

Type of infection	Dose of Vabomere (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
Infections due to aerobic Gram-negative organisms in patients with limited treatment options	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

Vaborem is administered by intravenous infusion over 3 hours.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	04 December 2019
Formal control completed	17 December 2019
List of Questions (LoQ)	15 April 2020
Answers to LoQ	14 July 2020
Predecision	26 November 2020
Answers to Predecision	25 January 2021
Labelling corrections	20 April 2021
Answers to Labelling corrections	20 May 2021
Final Decision	01 July 2021
Decision	approval

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3 Medical Context

The prevalence of infections caused by drug-resistant Gram-negative bacteria is increasing world-wide.

β-lactamases are enzymes able to hydrolyse β-lactams and are considered to be the most important and clinically relevant mechanism of resistance in Gram-negative bacteria. Genes encoding β-lactamases may be present on the bacterial chromosome, and are also often found on mobile genetic elements such as plasmids and transposons, allowing for both horizontal and vertical genetic transmission (Wong & van Duin, 2017). Of particular concern are carbapenemases, β-lactamases that hydrolyse carbapenems. This results in reduced susceptibility and resistance to carbapenems and other β-lactams. The most important carbapenemases include:

- *Klebsiella pneumoniae* carbapenemase (KPC, Ambler class A)
- Verona integron-encoded metallo-β-lactamase (VIM, Ambler class B)
- OXA-type carbapenemase (OXA-48, Ambler class D)
- New Delhi metallo-β-lactamase (NDM, Ambler class B)

The remaining treatment options for infections caused by carbapenem-resistant or carbapenemase-producing bacteria (in many cases carbapenem-resistant or carbapenemase-producing *Enterobacteriaceae* [CRE or CPE, respectively]) are very limited. The prevalence of such infections is increasing world-wide, and they are associated with high morbidity, attributable mortality and an increased duration of hospitalisation and higher healthcare costs (Magiorakos et al., 2017; Wong & van Duin, 2017). At present, treatment options include (combinations of) colistin, aminoglycosides, tigecycline and fosfomycin. It has been estimated that the mortality rate of these infections ranges between 32-44% (Wong & van Duin, 2017; ECDC, 2018).

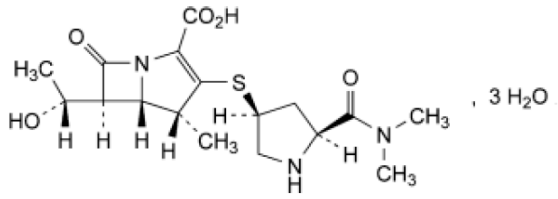
In Switzerland, as in the rest of the world, the use of carbapenems has increased in recent years. Carbapenem resistance is still relatively rare in Switzerland: 0.1% in *Escherichia coli* and 0.3% in *Klebsiella pneumoniae (*2017). For *Escherichia coli* this is largely comparable to the situation in the rest of Europe. However, for *Klebsiella pneumoniae* much higher resistance rates were observed in southern European countries (Anresis data: Gasser, Schrenzel & Kronenberg, 2018).

4 Quality Aspects

4.1 Drug Substance

Drug Substance – Meropenem trihydrate

INN: Meropenem
Chemical name: (4R,5S,6S)-3-[[(3S,5S)-5-[(Dimethylamino)carbonyl]pyrrolidin-3-yl]sulfanyl]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate
Molecular formula: $C_{17}H_{25}N_3O_5S\ 3H_2O$
Molecular mass: 437.5 g/mol
Molecular structure:



Meropenem is a well-known active substance and is monographed in the European Pharmacopoeia. The manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) by the EDQM for meropenem.

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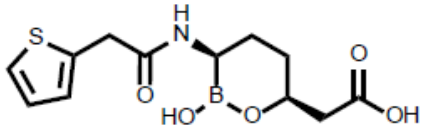
Meropenem appears as white or light yellow, crystalline powder. It is nonhygroscopic and is sparingly soluble in water. The molecule has 6 asymmetric carbon atoms. Only one crystal form of meropenem trihydrate is manufactured by the active substance manufacturer. Meropenem is supplied as sterile material.
The specifications are according to the Ph. Eur. monograph with additional tests for acetone, palladium and sterility.
Reference is made to the CEP, according to which the re-test period is 2 years.

Drug Substance - Vaborbactam

INN: Vaborbactam
Chemical name: (3R,6S)-2-hydroxy-3-[[2-(2-thienyl)acetyl]amino]-1,2-oxaborinane-6-acetic acid
Molecular formula: $C_{12}H_{16}BNO_5S$
Molecular mass: 297.14 g/mol
Molecular structure:



Vaborbactam is a white to off-white crystalline solid. Vaborbactam is slightly soluble in water and freely soluble in methanol. It is essentially insoluble in other organic solvents. Vaborbactam is nonhygroscopic. The structure assignment is supported by the results of single crystal X-ray analysis.
The drug substance is manufactured by a multiple-step chemical synthesis with final isolation by crystallisation. The sterile drug substance is manufactured as the crystalline form A.
The drug substance specification includes relevant tests for proper quality control, encompassing tests relating to identification, assay, impurities, specific optical rotation, sterility and bacterial endotoxins.
Appropriate stability data have been presented and justify the established re-test period.

4.2 Drug Product

Meropenem-Vaborbactam for Injection drug product is a sterile powder blend, filled in single-use glass vials. Each vial delivers 1000 mg each of meropenem and vaborbactam.
The composition of the drug product is adequately described, qualitatively and quantitatively.
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including a risk assessment for the attributes of the drug substance, excipients and the manufacturing process for potential impact on the critical quality attributes (CQA(s)) of the intended commercial drug product.
The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.
Adequate validation data pertaining to the commercial manufacturing process are available.
The drug product specification covers relevant physicochemical characteristics; identification, assay, purity, sterility and bacterial endotoxin tests are included as well. They allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.
The container closure system for Meropenem-Vaborbactam for Injection is a 50 mL glass vial sealed with a rubber stopper and capped with an aluminium seal.
Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. The data show good stability of the finished product and allow for a distinct assignment of the shelf life.

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Meropenem-Vaborbactam for Injection is intended for intravenous administration after reconstitution with 20 mL sodium chloride 9 mg/ml (0.9%) solution for injection (normal saline) and further dilution with normal saline in an infusion bag prior to administration. The stability of the constituted solution (in vial) as well as product further diluted in an infusion bag (IV bag) has been evaluated.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Vaborem, powder for concentrate for solution for infusion, the Preclinical Review Division conducted an abridged evaluation based on the European Medicines Agency (EMA) assessment report (EMA/CHMP/785079/2017, dated 20 September 2018) provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Vaborem® (meropenem/vaborbactam) in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. The safety margins are considered low but sufficient. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

ADME

Absorption

As meropenem/vaborbactam is administered intravenously, no bioequivalence or bioavailability studies were required.

Dose proportionality

After administration of single and multiple doses in the range of 250 mg to 2000 mg (three times a day (TID) for multiple dosing) of vaborbactam alone there was a dose-proportional increase in its exposure. This was also the case after co-administration with meropenem.

Pharmacokinetics after multiple dosing

After administration of doses of 250 mg to 2000 mg vaborbactam TID for 7 days, no accumulation was observed in subjects with normal renal function. The linearity index was close to 1, indicating time-independent pharmacokinetics. Steady state was reached on the second day of TID dosing.

Distribution

The vaborbactam Vc after single and multiple dosing was between 20 and 33 L. The vaborbactam plasma protein binding was between 29% and 37%. It was independent of the vaborbactam concentration in the investigated concentration range of 1 to 50 µg/mL.

The ratio of meropenem concentrations in epithelial lining fluid (ELF) to the total meropenem plasma concentrations was 0.525 at 1.5 h post end of infusion and increased over time to 2.133 at 8 h post end of infusion. All meropenem concentrations in alveolar macrophages (AM) were below the limit of quantitation of the LC-MS/MS assay used.

The ratio of vaborbactam concentrations in ELF and AM to the total vaborbactam plasma concentrations was 0.45 and 0.062 at 1.5 h post end of infusion, respectively. It increased over time to 1.0 and 1.6 at 8 h post end of infusion, respectively.

Metabolism

As vaborbactam was not metabolised *in vitro* and was almost completely excreted unchanged in urine *in vivo*, a clinical metabolism study was not required.

Elimination

After single and multiple dosing, the vaborbactam half-life was about 1.5 h. More than 80% of the administered dose was excreted unchanged in urine. Renal clearance was about 12 L/h, indicating active renal secretion. Nonrenal clearance was about 1 - 2 L/h, i.e. renal excretion was the major route of elimination of vaborbactam.

Special Populations

As expected, **renal function** had a considerable impact on both meropenem and vaborbactam pharmacokinetics.

Meropenem: mild renal impairment had no major impact on meropenem exposure. The increase in Cmax was < 2-fold in all renal function groups. AUCinf showed a 2.07-fold, 4.63-fold and 3.28-fold increase in subjects with moderate or severe renal impairment and subjects with end-stage renal disease (ESRD) if meropenem/vaborbactam was given prior to haemodialysis. If meropenem/vaborbactam was given after dialysis, meropenem AUCinf showed a 7.22-fold increase compared to subjects with normal renal function. The meropenem half-life increased with decreasing renal function from 1.28 h in subjects with normal renal function to 5.71 h in subjects with severe renal impairment. In subjects with ESRD, it was 9.11 h and 9.28 h if meropenem/vaborbactam was given with and without dialysis. Dialysis caused a 2.21-fold increase in total meropenem clearance.

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Vaborbactam: mild renal impairment had no major impact on vaborbactam exposure. The increase in Cmax was ≤ 2-fold in all renal function groups. AUCinf showed a 2.31-fold, 7.81-fold and 10.2-fold increase in subjects with moderate or severe renal impairment and subjects with ESRD if meropenem/vaborbactam was given prior to haemodialysis. If meropenem/vaborbactam was given after dialysis, vaborbactam AUCinf showed a 37.5-fold increase compared to subjects with normal renal function. The vaborbactam half-life increased with decreasing renal function from 1.86 h in subjects with normal renal function to 11.7 h in subjects with severe renal impairment. In subjects with ESRD, it was 45.7 h and 54.3 h if meropenem/vaborbactam was given with and without dialysis. Dialysis caused a 5.1-fold increase in total vaborbactam clearance. The impact of renal function was greater on vaborbactam PK than on meropenem PK.

The predominant impact of renal function on the pharmacokinetics of meropenem and vaborbactam was confirmed in a pop PK analysis.

Apart from renal function, the potential impact of age, gender, height or weight and race on the pharmacokinetics of meropenem and vaborbactam was investigated in the pop PK analysis. The range of age, weight and eGFR of the subjects/patients included in the pop PK dataset was sufficiently wide to detect potential covariate effects.

The structural models for both meropenem and vaborbactam were 2-compartment models with zero order input and first order elimination. The relationship between clearance and eGFR was described by a sigmoidal Emax model. Because of the known major impact of renal function on the pharmacokinetics of both compounds, this covariate relationship was included in the base models.

The relationship between eGFR and total clearance was similar for meropenem and vaborbactam, indicating that similar dose adjustments would be likely to accommodate both compounds.

After accounting for renal function, body size, age, gender and race had no major impact on meropenem or vaborbactam PK.

Both models described the data quite well in all renal function groups.

Compared to healthy subjects, infected patients had up to 2-fold and up to 3.4-fold meropenem or vaborbactam exposure, respectively.

The proposed dose adjustments for patients with impaired renal function as described in the information for healthcare professionals (see Chapter 8.1 of this report) were not based on the results of the dedicated Phase 1 “renal impairment study” but on pop PKPD simulations of target attainment.

As both meropenem and vaborbactam are almost exclusively eliminated by renal excretion, a study in subjects with hepatic impairment was not necessary. No dose adjustments for hepatic function are required.

Interactions
Dose adjustments and recommendations with regard to concomitant medications are addressed in the attached information for healthcare professionals; see Chapter 8.1 of this report.

In vitro data – Inhibition of hepatic CYPs
Based on the available *in vitro* data, the direct inhibition of CYP2B6, CYP2C19 and possibly CYP3A4 at therapeutic vaborbactam exposures could not be excluded. There was no evidence of time-dependent inhibition of CYPs.

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In vitro data – Induction of hepatic CYPs
Vaborbactam induced CYP2B6 and 3A4 *in vitro*.

In vitro data – Interactions with transporters
Vaborbactam was a substrate for OAT3. This transporter mediates the active renal secretion of vaborbactam. The inhibition of Pgp, OATP1B1 and OATP1B3 by vaborbactam at therapeutic exposures could not be excluded.

Clinical data
There were no mutual pharmacokinetic interactions between vaborbactam and meropenem. The pharmacokinetics of vaborbactam and meropenem were similar to the extent that both compounds had a short half-life and a renal clearance of similar magnitude. The percentage of the administered dose excreted as unchanged drug in urine was slightly lower (about 60% versus 80%) for meropenem compared to vaborbactam.

Pharmacodynamics
Meropenem/vaborbactam caused a concentration-dependent QTcF prolongation. At the therapeutic dose, the upper limit of the ΔΔQTcF least squares mean 90% confidence interval never exceeded 10 ms. At the supratherapeutic dose, the effect of meropenem/vaborbactam on ΔΔQTcF at tmax was comparable to moxifloxacin, which showed the expected effect, i.e. assay sensitivity was demonstrated. The results of the exposure-response analysis and the “conventional” statistical analysis of the data were in good agreement. The estimated “10 ms threshold” for vaborbactam was a Cmax of 193 µg/mL.

The supratherapeutic dose administered in the tQT study was 6 g/6 g meropenem/vaborbactam infused over 2 hours instead of 3 hours, resulting in a 4.13- fold and 4.3-fold higher meropenem and vaborbactam Cmax, respectively. The supratherapeutic dose for the tQT study was selected to cover the “worst case scenario” of meropenem/vaborbactam steady state exposure in subjects with severe renal impairment without dose adjustments.

Simulations of the meropenem and vaborbactam Cmax in patients with different degrees of renal impairment after the proposed dosing regimen indicated that the meropenem exposure achieved in the tQT study covered the mean Cmax expected in patients. However, the estimated vaborbactam Cmax,ss in patients with ESRD or severe renal impairment exceeded or was very close to the “10 ms threshold” estimated in the tQT study. This means that patients with ESRD or severe renal impairment may reach vaborbactam Cmax values that cause QTc prolongation despite the dose adjustments.

6.2 Dose Finding and Dose Recommendation

No dose finding studies with Vaborem were performed. The doses of meropenem and vaborbactam were chosen based on PKPD studies in animal and *in vitro* models of infection.

The proposed dose for meropenem is within the approved dosing range for meropenem as monotherapy. However, a longer infusion time is proposed. Based on PKPD targets known for meropenem and target attainment analysis using human plasma exposures and minimum inhibitory concentration (MIC) distributions from recent surveillance studies, the prolonged infusion time resulted in improved target attainment. The justification for the meropenem dose used in the Phase 3 studies was accepted. In addition, adequate efficacy and safety were shown for the chosen meropenem-dose in the treatment of complicated urinary tract infections (cUTI).

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6.3 Efficacy

The evaluation of the efficacy data of this application was carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment reports and respective product information from the EMA and FDA were used as a basis for the clinical evaluation.

The indication complicated urinary tract infections (cUTI), including acute pyelonephritis (AP) was supported by study 505, a randomised, double-blind, double-dummy, non-inferiority study evaluating efficacy, safety and tolerability of meropenem-vaborbactam compared to piperacillin/tazobactam in the treatment of adults with cUTI or AP. For details, see the information for healthcare professionals and the assessment reports of the EMA and FDA.

The assessment focused on the requested indications complicated intra-abdominal infections (cIAI) and hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), as well as the treatment of infections caused by aerobic Gram-negative bacteria in patients with limited treatment options. Efficacy in those indications was supported by study 506, a Phase 3, randomised, open-label trial of meropenem-vaborbactam versus best available therapy (BAT) in the treatment of cUTI, cIAI, HABP/VABP and bacteraemia suspected or known to be caused by carbapenem-resistant Enterobacteriaceae (CRE). In this study, patients were randomised 2:1 to meropenem-vaborbactam (n=52) or BAT (n=25).

The baseline characteristics of the m-MITT population (microbiological modified intention to treat) were largely comparable between the treatment groups. In both groups, 87% of the patients were white and 46% were female. The mean age was 63 years, and 49% and 26% of the patients were older than 65 and 75 years, respectively, in the meropenem-vaborbactam group versus 42% older than 65 years and 21% older than 75 years in the BAT group. The mean body mass index in both groups was approximately 27.6 kg/m^2. The majority of patients were enrolled in Europe and North America.

At baseline, 37% in the meropenem-vaborbactam group and 47% in the BAT group had diabetes mellitus, 49% in the meropenem-vaborbactam group and 42% in the BAT group met the criteria for systemic inflammatory response syndrome (SIRS), and 77% in the meropenem-vaborbactam group and 74% in the BAT group had a Charlson comorbidity index of ≥5. Most subjects (68% in the m-MITT population) in the BAT group received combination antibiotic therapy. The most frequently used antibiotics in combination antibiotic therapy were carbapenems (42% in the m-MITT population).

The primary efficacy endpoints were defined by indication (all-cause mortality for HAP, including VAP, and bacteraemia; eradication at test of cure (TOC)/overall success at end of treatment (EOT) for cIUI, including AP; and clinical cure at TOC for cIAI) and analysed for the microbiologically modified intention-to-treat population with carbapenem-resistant Enterobacteriaceae (mCRE-MITT) and the m-MITT population. Given the limited number of patients per indication, no statistical analysis was performed. Although this study was not designed for inferential testing, a Data Safety Monitoring Board (DSMB) recommended early study termination due to evidence of benefit in the meropenem-vaborbactam group.

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Overview of Efficacy Results in Study 506

HAP/VAP			
All-cause mortality at Day 28	m-MITT	0/5 (0)	1/1 (100)
	mCRE-ITT	0/4 (0)	1/1 (100)
Bacteremia			
All-cause mortality at Day 28	m-MITT	4/15 (26.7)	3/8 (37.5)
	mCRE-ITT	4/14 (28.6)	3/8 (37.5)
cUTI or AP			
Overall success at TOC [3]	m-MITT	4/ 13 (30.8)	4/8 (50.0)
	mCRE-ITT	4/ 12 (33.3)	2/4 (50.0)
Microbial Eradication at TOC [4]	m-MITT	3/13 (23.1)	2/8 (25.0)
	mCRE-ITT	3/12 (25.0)	2/4 (50.0)
cIAI			
Clinical cure at TOC [1]	m-MITT	2/2 (100)	0/2 (0)
	mCRE-ITT	2/2 (100)	0/2 (0)

[1] Defined as complete resolution or significant improvement of the baseline signs and symptoms such that no further surgical intervention or antimicrobial therapy was warranted.
[2] Includes microbial eradication and/or presumed eradication where presumed eradication was defined as clinical cure and microbiological indeterminate.
[3] Defined as a clinical outcome of Cure and microbiologic outcome of Eradication.
[4] $<10^4$ CFU/mL of urine.

The overall results in all infection types combined can be considered indicative of a benefit of meropenem-vaborbactam at the proposed dose in the treatment of infections caused by carbapenem-resistant Enterobacteriaceae. However, this study does not allow reliable conclusions to be drawn on efficacy, and thereby on the adequacy of the vaborbactam dose, in the separate infection types.

As meropenem is approved as monotherapy for the treatment of intra-abdominal infections and lower respiratory tract infections, it can be assumed that appropriate concentrations of meropenem are reached for a sufficient duration at the infection sites. There is insufficient efficacy data to confirm this for the proposed dose and prolonged duration compared to what is approved for meropenem monotherapy. However, given that the new proposed dose with longer infusion time resulted in improved attainment of the pharmacodynamic target, it can be assumed that the adjusted dose will not negatively impact efficacy.

For vaborbactam, it is acknowledged that the preclinical data and PKPD analyses are supportive of efficacy of vaborbactam at the proposed dose. Based on similar properties of vaborbactam as compared to meropenem, and similar drug properties in comparison to drugs known to penetrate well into peritoneal fluid, it is expected that adequate concentrations of vaborbactam will be reached in the extracellular fluid and peritoneal fluid for the treatment of cIAI caused by CRE. Additional simulations to evaluate PKPD target attainment based on free-drug plasma PKPD targets and ELF exposures provide further support for the use of meropenem-vaborbactam in the treatment of HAP/VAP. However, some uncertainties remain, as PKPD targets for ELF are not known and PK and penetration of meropenem and vaborbactam may be altered in patients with severe or critical HAP/VAP infection.

According to the *EMA Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections*, to support an indication of bacteraemia, comparable efficacy in patients with and without bacteraemia should be demonstrated. Few patients with bacteraemia at baseline receiving meropenem-vaborbactam (n=12) were included in study 505. Furthermore, due to the design and limited number of patients in study 506, no reliable conclusions can be drawn on efficacy in patients with bacteraemia not associated with cUTI/AP, cIAI or HAP/VAP caused by CRE.

Overall, based on all the available data and due to the lack of tissue-specific PKPD targets, it cannot be assumed that adequate concentrations of vaborbactam will be reached at infection sites not discussed in this application. However, there is a clear need for treatment options for infections caused by CRE. Furthermore, FDA and EMA guidelines acknowledge the difficulties in conducting adequate studies to evaluate efficacy and safety of antibiotics in the treatment of such infections. It is stressed that, in this case, the totality of the data should be taken into account, and support for a benefit in the treatment of infections caused by multidrug resistance (MDR) will mainly rely on results

of PKPD analyses. In view of these recommendations, and despite some remaining uncertainties, it is considered that the available data support the approval of Vaborem. The indication was adjusted to ensure the appropriate use of Vaborem (i.e. in patients for whom the empirical treatment usually recommended is not considered suitable). In addition, the limitations of the data were included in the information for healthcare professionals.

6.4 Safety

The evaluation of the safety data of this application was carried out in reliance on previous regulatory decisions by the EMA and FDA. For details, see the information for healthcare professionals and the assessment reports of the EMA and FDA.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

The prevalence of infections caused by carbapenem-resistant or carbapenemase-producing bacteria is increasing world-wide. These infections are associated with high morbidity, attributable mortality, an increased duration of hospitalisation and higher healthcare costs (Magiorakos et al., 2017; Wong & van Duin, 2017). As the treatment options for such infections are very limited, there is a need for effective treatments for carbapenem-resistant Enterobacteriaceae infections.

Beneficial effects

In vitro data and data from animal infection models demonstrated that vaborbactam preserved the activity of meropenem against *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacteriaceae.

Both meropenem and vaborbactam have similar, linear and time-independent pharmacokinetics in the therapeutic dose range. No accumulation occurred after multiple TID dosing in subjects with normal renal function. Both compounds penetrated into ELF. Vaborbactam was not metabolised but excreted unchanged in urine. There were no mutual pharmacokinetic interactions between the two compounds. No dose adjustments for hepatic impairment were required. After accounting for renal function, no dose adjustments for age, weight, gender or race were required.

Meropenem-vaborbactam showed high efficacy in the treatment of cUTI, including acute pyelonephritis. Non-inferiority to piperacillin/tazobactam was demonstrated in a randomised, double-blind, double-dummy, non-inferiority study.

Findings from a small Phase 3, randomised, open-label trial of meropenem-vaborbactam versus best available therapy (BAT) suggested a benefit of meropenem-vaborbactam in the treatment of cUTI, cIAI, HABP/VABP and bacteraemia suspected or known to be caused by carbapenem-resistant Enterobacteriaceae (CRE). Although this study was not designed for inferential testing, a DSMB recommended early study termination due to evidence of benefit in the meropenem-vaborbactam group.

Uncertainties regarding beneficial effects

The impact of hepatic impairment on vaborbactam PK was not formally studied. However, as vaborbactam is almost completely excreted unchanged in urine and has low plasma protein binding, hepatic impairment is unlikely to affect its pharmacokinetics.

Studies 505 and 506 do not allow reliable conclusions on the efficacy and safety of meropenem-vaborbactam in the treatment of cUTI/AP, cIAI, HAP/VAP and bacteraemia caused by CRE due to the limited number of patients with these infections included in the studies. Efficacy in these infections is assumed based on the efficacy of meropenem monotherapy and PKPD analyses.

Few patients with bacteraemia at baseline were included in study 505, and the findings in study 506 can only be considered suggestive of efficacy of meropenem-vaborbactam in bacteraemia.

Efficacy and safety of meropenem-vaborbactam in the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options other than those evaluated in the current

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application cannot be assumed due to the uncertainties related to PK and PKPD analyses and the lack of efficacy data.

Unfavourable effects

Dose adjustments are required for renal function.

Meropenem/vaborbactam caused a concentration-dependent QTc prolongation. The simulations of vaborbactam exposure in patients with different degrees of renal impairment after the proposed dosing regimen indicated that patients with ESRD or severe renal impairment may reach vaborbactam Cmax values that cause QTc prolongation despite the dose adjustments.

The safety profile of meropenem is already well-established. The most frequently observed AEs included headache, diarrhoea, infusion-site phlebitis and nausea. Regarding the safety profile of meropenem-vaborbactam, no major differences to the comparator arms or to meropenem monotherapy were observed.

Uncertainties regarding unfavourable effects

There remains some uncertainty regarding the safety profile of meropenem-vaborbactam, as the safety database is not large enough to capture less frequent adverse events (AEs).

Conclusions

There were no major issues associated with meropenem/vaborbactam pharmacokinetics and pharmacodynamics. The simulated dosing recommendations for patients with impaired renal function indicated a high probability of target attainment across all renal function groups, even for problematic bacteria like *Pseudomonas aeruginosa*.

Efficacy and safety of meropenem-vaborbactam in the treatment of cUTI/AP, cIAI, HAP/VAP caused by CRE and bacteraemia associated with one of these infections can be assumed based on the efficacy and safety of meropenem monotherapy and the available preclinical, PK and PKPD data for meropenem-vaborbactam. This was not fully confirmed by efficacy and safety data due to the limited number of patients with these infections included in the submitted studies.

However, based on the totality of the data, and in view of the need for treatment options for patients with infections caused by CRE and the difficulties of evaluating efficacy and safety in these relatively rare infections, Vaborem can be approved. The uncertainties regarding the data are included in the information for healthcare professionals.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Vaborem, powder for concentrate for solution for infusion was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

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

Composition

Active substances

Meropenemum ut Meropenemi trihydras, Vaborbactamum

Excipients

Natrii carbonas anhydricus
Each vial contains 10.9 mmol (250 mg) of sodium.

Pharmaceutical form and active substance quantity per unit

Powder for concentrate for solution for infusion.
White to light yellow powder.
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 “other information” *Instructions for handling*).

Indications/Uses

Vaborem is indicated for the treatment of the following infections in adults only indicated if it is established or strongly suspected after microbiological sensitivity testing that the infection is caused by sensitive bacteria (see “warnings and precautions” and “properties/effects”):

- 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.

To prevent rapid development of resistance to Vaborem, Vaborem must not be used for the treatment of such infections unless the antibiotics recommended for empirical initial treatment of these infections are not considered appropriate (see “Warnings and precautions”). Consideration should be given to official guidance on the appropriate use of antibacterial agents.

It is therefore recommended that the decision to prescribe Vaborem and initiation of therapy occur in a hospital setting under the direction of a specialist, e.g. a specialist in infectious diseases.

Dosage/Administration

Usual dosage

Table 1 shows the recommended intravenous dose for patients with a creatinine clearance (CrCl) ≥40 ml/min (see “warnings and precautions” and “properties/effects”).

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 dosage instructions

Patients with impaired hepatic function

No dose adjustment is required in patients with hepatic impairment (see “warnings and precautions” and “pharmacokinetics”).

Patients with impaired renal function

Table 2 shows the recommended dose adjustments for patients with a CrCl ≤39 ml/min. Meropenem and vaborbactam are removed by haemodialysis (see “pharmacokinetics”). 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

Elderly patients

No dose adjustment based on age is required (see “pharmacokinetics”).

Children and adolescents

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.

Mode 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 “other information”)

Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in “composition”.
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).

Warnings and precautions

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions have been reported with meropenem and/or meropenem/vaborbactam (see “contraindications” and “undesirable effects”).

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.

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 taking beta-lactam antibiotics, including Vaborem (see also “Undesirable effects”). When signs or symptoms of SCAR are seen, Vaborem must be discontinued immediately and an alternative treatment should be considered.
If a severe allergic reaction occurs, treatment with Vaborem must be discontinued immediately and adequate emergency measures must be initiated.

Seizures
Seizures have been reported during treatment with meropenem (see “undesirable effects”).

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 “dosage/administration”). Alternatively, meropenem/vaborbactam should be discontinued (see “interactions”).

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 “undesirable effects”).

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

ESRD or severe renal impairment
Plasma concentrations of vaborbactam in patients with ESRD or severe renal impairment are expected to be in the range that resulted in QTcF prolongation in the tQT study. Therefore, Vaborem

should be used with caution in patients with ESRD or severe renal impairment with known risk factors for prolongation of the QT interval and/or concomitant use of drugs known to prolong the QT interval (see properties/effects).

Antiglobulin test (Coombs test) seroconversion

A positive direct or indirect Coombs test may develop during treatment with meropenem/vaborbactam as seen with meropenem (see “undesirable effects”).

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 “undesirable effects”). 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 “interactions”).

Limitations of the clinical data

The use of Vaborem to treat patients with complicated intra-abdominal infections, hospital-acquired pneumonia, including ventilator-associated pneumonia, or bacteraemia that occurs in association with any of the infections indicated, or is suspected to be associated with any of the infections indicated, is based on experience with meropenem alone, pharmacokinetic-pharmacodynamic analyses of meropenem/vaborbactam and on limited data from a randomised clinical trial 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 “properties/effects”).

Spectrum of activity of meropenem/vaborbactam

Meropenem does not have activity against methicillin-resistant *Staphylococcus aureus* (MSRA) 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 “properties/effects”).

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, corresponding to 12,5% of the maximum daily sodium intake recommended by the WHO for an adult of 2 g.
Caution is indicated when switching the treatment to a different medicinal product with the same active substance. The patient should be monitored appropriately.

Interactions

In vitro data suggest that vaborbactam and meropenem may induce CYP3A4 and CYP2B6. When administering meropenem/vaborbactam concomitantly with medicinal products that are predominantly metabolised by CYP3A4 and CYP2B6, there is a risk that a potential interaction would result in decreased plasma concentrations.

In vitro data suggest that vaborbactam may inhibit OATP1B1. When administering meropenem/vaborbactam concomitantly with medicinal products that are substrates of OATP1B1, there is a risk that a potential interaction would result in increased plasma concentrations of the co-administered drug.

No mutual pharmacokinetic interactions have been observed between meropenem and vaborbactam.

Effect of Vaborem on other medicinal products

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 “warnings and precautions”).

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.

Effect of other medicinal products on Vaborem

Both meropenem and vaborbactam are substrate 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.

Pregnancy, 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 “preclinical data”).
As a precautionary measure, it is preferable to avoid the use of Vaborem during pregnancy.

Lactation

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 “preclinical data”).

Effects on ability to drive and use machines

No corresponding studies have been performed. Seizures have been reported during treatment with meropenem alone, especially in patients treated with anticonvulsants (see “warnings and precaution”). Meropenem/vaborbactam may cause headache, paraesthesia, lethargy and dizziness (see “undesirable effects”). Therefore, caution should be exercised when driving or using machines.

Undesirable effects

Summary of the safety profile

The most common adverse reactions that occurred among 322 patients from the pooled Phase 3 trials 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 trials 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 trials 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		Agranulocytosis Haemolytic anaemia

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)
		Eosinophilia Thrombocytopenia		
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	
Cardiac disorders		Blood creatine phosphokinase increased		
Vascular disorders	Hypotension	Phlebitis Vascular pain		
Respiratory, thoracic and mediastinal disorders		Bronchospasm		

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)
Gastrointestinal disorders	Diarrhoea Nausea Vomiting	Abdominal distension Abdominal pain		
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),

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)
				Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) Acute generalised exanthematous pustulosis (AGEP) (see "Warnings and precautions")
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 Infusion site erythema Injection site phlebitis		

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 thrombosis Pain		
Investigations				Direct and indirect Coombs test positive
Injury, poisoning and procedural complications		Infusion related reaction		

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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 “undesirable effects”, 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 heamodialysis. 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.

Properties/Effects

ATC code

J01DH52

Mechanism of action

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) 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.

Pharmacodynamics

Clinical efficacy

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
- Enterobacter 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

Cardiac Electrophysiology

In a randomized, positive- and placebo-controlled, thorough QT/QTc study the Vaborem therapeutic dose (2 g/2 g infused over 6 hours) and supratherapeutic dose (6 g/6 g infused over 2 hours) had no relevant effects on heart rate, PR and QRS. Vaborem caused a concentration dependent QTcF prolongation that only at the supratherapeutic dose might be of clinical relevance.

Clinical Efficacy

The efficacy of Vaborem was established in two randomized clinical trials performed in patients with cUTI, including pyelonephritis (Trial 1) and in patients with severe gram-negative infections, including cUTI/AP, cIAI, HABP, VABP, and bacteraemia, suspected or known to be caused by CRE (Trial 2). Trial 1 was a double-blind, double dummy trial comparing Vaborem (meropenem 2 grams and vaborbactam 2 grams) to piperacillin/tazobactam (piperacillin 4 grams/tazobactam 0.5 grams) intravenously every 8 hours; the switch to an oral antibacterial drug, such as levofloxacin was allowed after a minimum of 15 doses of IV therapy. Trial 2 was an open-label study comparing Vaborem (meropenem 2 grams and vaborbactam 2 grams) to best available treatment (BAT).

In trial 1, 272 patients with cUTI, including pyelonephritis were randomized to Vaborem and 273 to piperacillin/tazobactam intravenously every 8 hours.
Patient demographic and baseline characteristics were balanced between treatment groups in the microbiologically modified intent to treat population (m-MITT), which included all randomized patients who received any study drug and had at least 1 baseline uropathogen. Approximately 93% of patients were Caucasian and 66% were females in both treatment groups. The mean age was 54 years with 32% and 42% of patients older than 65 years and 14% and 21% older than 75 years in Vaborem and piperacillin/tazobactam treatment groups, respectively.
Mean body mass index was approximately 26.5 kg/m^2 in both treatment groups. Concomitant bacteraemia was identified in 12 (6%) and 15 (8%) patients at baseline in Vaborem and piperacillin/tazobactam treatment groups respectively. The proportion of patients with diabetes mellitus at baseline was 17% and 19% in Vaborem and piperacillin/tazobactam treatment groups, respectively. The majority of patients (approximately 90%) were enrolled from Europe, and approximately 2% of patients were enrolled from North America. Overall, in both treatment groups, 59% of patients had pyelonephritis and 40% had cUTI, with 21% and 19% of patients having a non-removable and removable source of infection, respectively.

Mean duration of IV treatment in both treatment groups was 8 days and mean total treatment duration (IV and oral) was 10 days; patients with baseline bacteraemia could receive up to 14 days of therapy. The primary endpoints were the eradication rates at test of cure (TOC) in m-MITT and ME populations. Efficacy was also assessed through the overall success, a composite outcome including both clinical (i.e., Cure or Improvement) and microbiologic (Eradication/presumed Eradication) at the EOIVT visit.

Table 4: Trial 1 Eradication Rate at TOC (m-MITT Population and ME Population) and Overall Success at EOIVT

Group/subgroup	Population	Vaborem n/N (%)	Piperacillin/ tazobactam n/N (%)	Treatment difference* (2-sided 95% CI)
Eradication Rate at TOC	m-MITT Pop.	128/192 (66.7%)	105/182 (57.7%)	9.0 (-0.9, 18.7)
	ME Pop.	118/178 (66.3%)	102/169 (60.4%)	5.9 (-4.2, 16.0)
Overall success at EOIVT	m-MITT Pop.	189/192 (98.4%)	171/182 (94.0%)	4.5 (0.7, 9.1)

Per EMA Criteria, a microbiologic outcome of Eradication is defined as the demonstration that the bacterial pathogen(s) found at baseline is reduced to $<10^3$ CFU/mL of urine.
Per FDA criteria, a microbiologic outcome of Eradication is defined as the demonstration that the bacterial pathogen(s) found at baseline is reduced to $<10^4$ CFU/mL of urine.
CI = confidence interval; cUTI = complicated urinary tract infection; m-MITT = microbiologically modified intention-to-treat; ME = microbiological evaluable; Pop = population; TOC = test of cure.
*Treatment difference, expressed as percentage, and CI based on Miettinen and Nuriminen method.
Microbiological Evaluable population included all subjects randomized who received at least one dose of study drug and met all of the following criteria: a) had a bacterial pathogen(s) of $\geq 10^5$ CFU/mL of urine at baseline urine culture for evaluation or have the same bacterial pathogen present in concurrent blood and urine cultures; b) had no key inclusion or exclusion violations; c) a clinical outcome (Cure, Improvement, or Failure) and microbiologic outcome (eradication or persistence) at end of intravenous treatment (EOIVT), unless criteria for Failure on clinical outcome were met at an earlier time point; d) received ≥80% and ≤120% of expected IV doses for the completed treatment duration, missed no more than one IV dose in the first 48 hours of treatment, and missed no more than two consecutive IV doses overall; e) received ≥6 doses of study drug if classified as a Failure on overall outcome or received ≥9 doses of study drug if classified as a Cure on overall outcome; and f) only had an identified gram-positive pathogen in the urine and had received >48 hours of an antibiotic with only gram-positive coverage will not be included in the m-MITT Population

The eradication rate in the m-MITT and ME populations in Vaborem-treated patients with concurrent bacteremia at baseline was 9/12 (75%) and 9/10 (90%), respectively.

Table 5: Trial 1 Success Rates per Baseline Pathogens (m-MITT Population, TOC visit)

Pathogen	Vaborem n/N (%)	Piperacillin/ tazobactam n/N (%)
Enterobacter Cloacae Species Complex	7/10 (70.0%)	3/5 (60.0%)
Enterococcus Faecalis	7/13 (53.9%)	11/14 (78.6%)
Escherichia Coli	99 /125 (79.2%)	85/117 (72.6%)
Klebsiella Pneumoniae	18/30 (60.0%)	15/28 (53.6%)
Proteus Mirabilis	3/6 (50.0%)	9/12 (75.0%)

Pseudomonas Aeruginosa	5/5 (100.0%)	4/10 (40.0%)

Only pathogens with a frequency of at least 15 are included.

In Trial 2, 77 patients were randomized, 52 to Vaborem and 25 to BAT. 34 with cUTI, 28 with bacteraemia, 8 with HABP/VABP, and 7 with cIAI. Gram-negative pathogens were isolated in patients who received the study drug at baseline (m-MITT Population) in 35 patients in the Vaborem group and 19 in the BAT group. Out of them, 32 in the Vaborem group and 15 in the BAT group had meropenem-resistant Enterobacteriaceae at Baseline (mCRE-MITT Population).

Patient demographic and baseline characteristics were mostly balanced between treatment groups in the m-MITT population. Approximately 87% of patients were white and 46% were females in both treatment groups (54% in the Vaborem and 32% in the BAT group). The mean age was 63 years with 49% and 42% of patients older than 65 years and 26% and 21% older than 75 years in Vaborem and BAT groups, respectively. Mean body mass index was approximately 27.6 kg/m^2 in both treatment groups.

The proportion of patients with diabetes mellitus at baseline was 37% and 47%, the proportion of patients meeting (systemic inflammatory response syndrome SIRS) at baseline was 49% and 42%, and the proportion of patients with a a Charlson comorbidity score of ≥5 was 77% and 74% in Vaborem and BAT groups, respectively. The majority of patients were enrolled from Europe (57%) and North America (30%).

Most subjects (68% in the m-MITT) in the BAT group received combination antibiotic therapy. Carbapenems were the most frequent antibiotics used in combination for subjects in the BAT group (42% in the m-MITT).

Efficacy data were analyzed for the microbiological Carbapenem-resistant Enterobacteriaceae Modified Intent-to-Treat (mCRE-MITT) and the m-MITT Populations. The primary efficacy endpoints were defined in the mCRE-MITT population by indication and are presented in the table below. The independent Data and Safety Monitoring Board advised discontinuing the study after reviewing safety and efficacy data (all indications) because the risk/benefit analysis did not support ongoing randomization of subjects to the BAT arm. Considering the limited number of patients per indication, no statistical analysis was performed.

Table 6: Trial 2 Overview of Efficacy Results by Indication

Indication	Endpoint	Population	Meropenem-Vaborbactam n (%)	BAT n (%)
HAP/VAP	All-cause mortality at Day 28	mCRE-ITT	0/4 (0)	1/1 (100.0)
		m-MITT	0/5 (0)	1/1 (100.0)
Bacteremia	All-cause mortality at Day 28	mCRE-ITT	4/14 (28.6)	3/8 (37.5)
		m-MITT	4/15 (26.7)	3/8 (37.5)
cUTI or AP	Overall success at TOC*	mCRE-ITT	4/12 (33.3)	2/4 (50.0)
		m-MITT	4/13 (30.8)	4/8 (50.0)
	Microbial Eradication at TOC†	mCRE-ITT	3/12 (25.0)	2/4 (50.0)
		m-MITT	3/13 (23.1)	2/8 (25.0)
cIAI	Clinical cure at TOC‡	mCRE-ITT	2/2 (100)	0/2 (0)

		m-MITT	2/2 (100)	0/2 (0)

* Overall Success is defined as a clinical outcome of Cure and microbiologic outcome of Eradication. Per FDA Criteria, a microbiologic outcome of eradication is defined as the demonstration that the bacterial pathogen(s) found at baseline is reduced to $<10^4$ CFU/mL of urine;
†Per EMA Criteria, a microbiologic outcome of eradication is defined as the demonstration that the bacterial pathogen(s) found at baseline is reduced to $<10^3$ CFU/mL of urine.
‡Defined as complete resolution or significant improvement of the baseline signs and symptoms such that no further surgical intervention or antimicrobial therapy was warranted.
AP = acute pyelonephritis; BAT = best available therapy; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; HAP = hospital-acquired bacterial pneumonia; mCRE-MITT = microbiological carbapenem-resistant Enterobacteriaceae Modified Intent-to-Treat; m-MITT = microbiological Modified Intent-to-Treat; TOC = Test of Cure; VAP = ventilator-acquired bacterial pneumonia.

Table 7: Trial 2 Success Rates per Baseline Pathogens (m-MITT Population, TOC visit)

Pathogen	**Vaborem n/N (%)**	**BAT n/N (%)**
Elizabethkingia Meningoseptica / *Elizabethkingia Anophelis* / *Elizabethkingia Miricola*	1/1 (100.0%)	0/0
Enterobacter Cloacae Species Complex	1/1 (100.0%)	2/2 (100.0%)
Enterococcus Faecalis	1/2 (50.0%)	0/0
Eterococcus Faecium	0/0	0/1 (0.0%)
Escherichia Coli	0/2 (0.0%)	1/4 (25.0%)
Klebsiella Pneumoniae	11/27 (40.7%)	4/13 (30.8%)
Proteus Mirabilis	0/0	0/2 (0.0%)
Providencia Stuartii	0/0	0/1 (0.0%)
Pseudomonas Aeruginosa	1/1 (100.0%)	0/0
Serratia Marcescens	0/0	0/1 (0.0%)
Unspeciated *coliform*	0/0	0/1 (0.0%)

Pharmacokinetics

Absorption

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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 18.6 L and 20 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.

Metabolism

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 Cmax 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.

Kinetics in specific patient groups

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.

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.

The results from a statistical evaluation (geometric mean ratios and 90% confidence intervals) comparing meropenem and vaborbactam PK parameters in subjects with renal impairment versus healthy controls has shown that a statistically significant increase in $AUC_{0\text{-}inf}$ and C_{max} was observed

for renal impairment groups when compared to healthy controls, assessed using the 90% CIs and significance boundaries of 0.80 to 1.25.

Table 8: Summary of the statistical comparison of meropenem and vaborbactam pharmacokinetic parameters between renal function groups

Drug	Parameter	Ratio of Geometric Means (90% confidence interval)		
		Mild versus Normal	Moderate versus Normal	Severe versus Normal
Meropenem	$AUC0\text{-}_{Inf}$ (µg•h/mL)	1.28 (0.999, 1.65)	2.07 (1.61, 2.65)	4.63 (3.6, 5.94)
	C_{max} (µg/mL)	1.19 (0.971, 1.45)	1.5 (1.23, 1.83)	1.65 (1.35, 2.02)
Vaborbactam	$AUC0\text{-}_{Inf}$ (µg•h/mL)	1.18 (0.880, 1.59)	2.32 (1.73, 3.11)	7.82 (5.83, 10.5)
	C_{max} (µg/mL)	1.08 (0.882, 1.31)	1.54 (1.26, 1.88)	1.66 (1.36, 2.03)

Elderly patients

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

Preclinical data

Safety Pharmacology

Meropenem or vaborbactam did not affect cardiovascular, respiratory, or central nervous system functions. No studies have been performed on the drug combination.

Repeat dose toxicity

No treatment related adverse effects were observed in 14 and 28 day studies from either vaborbactam or meropenem alone or in combination in rats; the systemic exposure in the 28 day studies at the highest non-toxic doses was about 1.3 fold higher for vaborbactam and 5-fold lower for meropenem than in humans at the clinical doses. 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; the systemic exposure at the non-toxic doses in the 28 day combination study was respectively 3.9 and 1.9-fold higher for vaborbactam and meropenem than in humans at the clinical doses.

Mutagenicity

No evidence of mutagenic or genotoxic potential was found in any of the tests conducted on meropenem, including, reverse mutation and induced mutation frequency tests in S. typhimurium and E. Coli (Ames test), gene mutation in cultured mammalian cells and in vivo micronucleus test in mice. Likewise, vaborbactam did not induce mutagenic or genotoxic effects in the Ames test, chromosome aberration test or in human lymphocytes in vitro and in vivo micronucleus test in mice. No tests have been performed on the combination meropenem/vaborbactam.

Carcinogenicity

Long-term studies with vaborem (meropenem/vaborbactam), vaborbactam or meropenem to investigate carcinogenic potential have not been performed.

Reproductive toxicity

Meropenem or vaborbactam did not impair rat male and female fertility, pregnancy and embryofetal viability. Meropenem did not display teratogenic effects and did not impact parturition in rats or monkeys, nor affected lactation and offspring development in rats. Likewise, there were no vaborbactam-related teratogenic effects in rats and rabbits, or adverse effects on parturition, lactation or offspring development in rats. In rabbits, the systemic exposure to vaborbactam at the highest non toxic dose was about 7-fold higher than in humans at the clinical doses. Studies on reproductive toxicity were not carried out with the combination meropenem/vaborbactam.

Juvenile toxicity

Meropenem alone, vaborbactam alone, or the combination meropenem/vaborbactam had no adverse effects in a 28 day study carried out in juvenile rats.

Other information

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 “other information”.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening

<u>After reconstitution</u>

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.

Special precautions for storage

Do not store above 25°C, store in the original package and out of reach of children.

Instructions for 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.

Following dilution, the infusion should be completed within 4 hours when stored at 25 C, or within 22 hours when refrigerated at 2 – 8°C.

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

Authorisation number

67797 (Swissmedic).

Packs

The medicinal product is supplied in packs of 6 vials.

Marketing authorisation holder

A. Menarini GmbH, Zurich

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