

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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.

Vaborem is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options (see sections 4.2, 4.4 and 5.1).

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

4.2 Posology and method of administration

Vaborem should be used to treat infections due to aerobic Gram-negative organisms in adult patients with limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases (see sections 4.4 and 5.1).

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/min¹

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
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

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/min¹

CrCl (ml/min) ¹	Recommended Dosage Regimen ²	Dosing Interval	Infusion Time
20 to 39	1 g/1 g	Every 8 hours	3 hours

CrCl (ml/min) ¹	Recommended Dosage Regimen ²	Dosing Interval	Infusion Time
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).

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ 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 ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)	Unknown (cannot be estimated from the available data)
Infections and infestations		<i>Clostridium difficile</i> 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	Convulsions	

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)
		Paraesthesia		
Vascular disorders	Hypotension	Phlebitis Vascular pain		
Respiratory, thoracic and mediastinal disorders		Bronchospasm		
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) Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) Acute generalised exanthematous pustulosis (AGEP) (see section 4.4)
Renal and urinary		Renal impairment		

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)
disorders		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 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 listed in [Appendix V](#).

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

Pharmacotheapeutic 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:

Organisms	Minimum Inhibitory Concentrations (mg/l)	
	Susceptible	Resistant
<i>Enterobacterales</i>	≤8 ¹	>8 ¹
<i>Pseudomonas aeruginosa</i>	≤8 ¹	>8 ¹

¹For 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*

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Vaborem in one or more subsets of the paediatric population in the treatment of infections due to Gram-negative bacteria (see section 4.2 for information on paediatric use).

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 ($t_{1/2}$) 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

4 years

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

Do not store above 25 °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. MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.
1, Avenue de la Gare
L-1611, Luxembourg
Luxembourg

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1334/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 November 2018

Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

ACS Dobfar, S.p.A.
Nucleo Industriale S. Atto
(loc. S. Nicolo' a Tordino)
64100 Teramo (TE)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains also sodium carbonate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
6 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after reconstitution and dilution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Menarini International O. L. S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1334/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Vaborem 1 g/1 g powder for concentrate
meropenem/vaborbactam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 g meropenem/1 g vaborbactam

3. LIST OF EXCIPIENTS

Sodium carbonate

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet.
Intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25° C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1334/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

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

meropenem/vaborbactam

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vaborem is and what it is used for
2. What you need to know before you are given Vaborem
3. How you will be given Vaborem
4. Possible side effects
5. How to store Vaborem
6. Contents of the pack and other information

1. What Vaborem is and what it is used for

What Vaborem is

Vaborem is an antibiotic medicine that contains two active substances: meropenem and vaborbactam.

- Meropenem belongs to group of antibiotics called “carbapenems”. It can kill many types of bacteria by preventing them from building the protective walls that surround their cells.
- Vaborbactam is a “beta lactamase inhibitor”. It blocks the action of an enzyme that allows some bacteria to resist the action of meropenem. This helps meropenem kill some bacteria that it cannot kill on its own.

What Vaborem is used for

Vaborem is used in adults to treat certain serious bacterial infections:

- of the bladder or kidneys (urinary tract infections)
- of the stomach and gut (intra-abdominal infections)
- of the lungs (pneumonia)

It is also used to treat infections

- of the blood associated with any of the infections mentioned above
- caused by bacteria that other antibiotics may not be able to kill

2. What you need to know before you are given Vaborem

You must not be given Vaborem if

- you are allergic to meropenem, vaborbactam or the other ingredients of this medicine (listed in section 6).
- you are allergic to other carbapenem antibiotics (the group to which meropenem belongs).
- you have ever had a severe allergic reaction to related antibiotics belonging to the beta-lactam group (including penicillins, cephalosporins or monobactams).

Warnings and precautions

Talk to your doctor or nurse before receiving Vaborem if:

- you have ever had any allergic reaction to other antibiotics belonging to the beta-lactam group (including carbapenems, penicillins, cephalosporins, or monobactams)
- you have ever developed severe diarrhoea during or after antibiotic treatment
- you have ever suffered from seizures

If any of the above apply to you or you are not sure, talk to your doctor or nurse before using Vaborem.

You may develop signs and symptoms of severe skin reactions (see section 4). If this happens talk to your doctor or nurse immediately so that they can treat the symptoms.

Talk to your doctor or nurse if you suffer from diarrhoea during your treatment.

This medicine can affect your liver. Your doctor may take some blood to check how well your liver is working while taking the medicine.

New infection

Although Vaborem can fight certain bacteria, there is a possibility that you may get a different infection caused by another organism during or after your treatment. Your doctor will monitor you closely for any new infections and give you another treatment if necessary.

Blood tests

Tell your doctor that you are taking Vaborem if you are going to have any blood tests. This is because you may get an abnormal result with something called a “Coombs test”. This test looks for the presence of antibodies that can destroy red blood cells or may be affected by the response of your immune system to Vaborem.

Children or adolescents

Vaborem should not be used in children or adolescents under 18 years of age. This is because it is not known if the medicine is safe to use in these age groups.

Other medicines and Vaborem

Tell your doctor if you are using, have recently used or might use any other medicines.

It is particularly important to tell your doctor if you are taking any of the following medicines:

- medicines used to treat epilepsy called valproic acid, sodium valproate or valpromide because Vaborem may decrease their effect
- a medicine for gout called probenecid
- oral anticoagulant medicines, such as warfarin (used to treat or prevent blood clots)
- hormonal oral contraceptives containing oestrogen and/or progesterone because Vaborem may decrease their effect. 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.
- medicines 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) because Vaborem may decrease their effect.

Tell your doctor before using Vaborem if any of the above apply to you.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before receiving this medicine.

As a precautionary measure, you should not be given this medicine during pregnancy.

It is important that you tell your doctor if you are breast-feeding or if you intend to breast-feed before receiving Vaborem. Small amounts of this medicine may pass into the breast milk and it may affect the baby. Therefore, you must discontinue breastfeeding before you are given Vaborem.

Driving and using machines

Vaborem may make you feel dizzy, sleepy and sluggish, give you a headache or tingling sensation (like “pins and needles”) or, in rare cases, cause a fit or seizure. This may affect your ability to drive, use tools or machines.

Vaborem contains sodium

This medicine contains 250 mg of sodium (main component of cooking salt) in each vial. This is equivalent to 12,5% of the recommended maximum daily dietary intake of sodium salt for an adult.

3. How you will be given Vaborem

The recommended dose is 2 vials (a total of 2 g meropenem and 2 g vaborbactam), given every 8 hours. Your doctor will decide how many days of treatment are needed, depending on the type of infection.

Vaborem will be given to you by a doctor or nurse by infusion (a drip) into a vein, lasting 3 hours.

Patients with kidney problems

If you have kidney problems, your doctor may lower your dose. Your doctor may also want to do some blood tests to see how well your kidneys are working.

If you are given more Vaborem than you should

Vaborem will be given to you by a doctor or a nurse, so it is unlikely you will be given the wrong dose. If you think you have been given too much Vaborem, tell your doctor or nurse straight away.

If you miss a dose of Vaborem

If you think you have missed a dose, tell your doctor or nurse straight away.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Tell your doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- Severe allergic reactions that could include sudden swelling of your lips, face, throat or tongue, difficulty swallowing or breathing or a severe rash or other severe skin reactions, or a decrease in blood pressure (which could make you feel faint or dizzy). Such reactions may be life-threatening.
- Diarrhoea that keeps getting worse or does not go away, or stools that contains blood or mucus – this may happen during or after treatment with Vaborem is stopped. It may be due to bacteria called *Clostridium difficile*. If this happens, do not take medicines that stop or slow bowel movement.

Other side effects

Tell your doctor or nurse if you notice any of the following side effects:

Common: (may affect up to 1 in 10 people)

- Increase in the number of platelets (a type of blood cell) – shown in blood tests
- Decrease in the amount of potassium or sugar- seen in blood tests
- Headache
- Low blood pressure
- Diarrhoea
- Feeling sick (nausea) or being sick (vomiting)
- Swelling, redness and/or pain around the needle where the medicine is given into a vein
- Fever
- Increase in the amount of enzymes produced by your liver called alanine aminotransferase or aspartate aminotransferase – shown in blood tests
- Increase in the level of an enzyme called alkaline phosphatase that may be a sign of your liver, gallbladder or bones working less well – shown in blood tests
- Increase in the level of an enzyme called lactate dehydrogenase that may be a sign of damage to some of your body organs – shown in blood tests

Uncommon: (may affect up to 1 in 100 people)

- Swelling and irritation in the large intestine or colon – this can cause diarrhoea, fever and stomach cramps and is due to another colon infection
- Fungal infections, including those of the vagina or mouth
- Decrease in the number of white blood cells or some types of white blood cells called neutrophils and a decrease of platelets – shown in blood tests
- Increase in a type of white blood cell called eosinophils – shown in blood tests
- Sudden and serious allergic reaction that needs urgent medical treatment and may include itching, skin color change, abdominal cramps, swelling, difficulty breathing, fainting and drop in blood pressure
- Less severe allergic reaction that may include redness, red bumps, flaking of the skin, itching, generally feeling unwell
- A feeling of being less hungry
- Increase in the amount of potassium or sugar – shown in blood tests
- Inability to sleep
- Seeing, hearing or sensing things that are not there
- Feeling dizzy
- Tremor or shaking
- A tingling feeling (pins and needles)
- A feeling of being sleepy and sluggish
- Swollen and red and irritated veins
- Painful veins
- Difficulty breathing
- Bloating or a feeling of fullness in your abdomen
- Stomach pain
- Itchy skin
- Rash
- Raised itchy skin rash (“hives”)
- Difficulty to control the bladder
- Reduction in the way your kidneys work
- Abnormal feeling in the chest
- The following reactions may develop, alone or in combination, where Vaborem is given into a vein: reddened skin (erythema); hot, tender and swollen vein around the needle (phlebitis); a blood clot in the vein where the needle was put through your skin (infusion site thrombosis)
- Pain

- Increase in the level of a substance in the blood called creatine phosphokinase that is a sign of possible damage to certain tissues such as your muscles and/or other organs – shown in blood tests
- Increase in the level of a substance in the blood called bilirubin that is a sign of possible damage to your red blood cells or that your liver is working less well – shown in blood tests
- Increase in the level of some types of substances in the blood called urea and creatinine that are signs that your kidneys are working less well – shown in blood tests
- Reaction that occurs during or shortly after Vaborem is given that presents as a malaise (generally feeling unwell) possibly with any of the following: reduced blood pressure, nausea, vomiting, abdominal cramps, fever, flushing, rapid heart beats or difficulty to breathe, headache

Rare (may affect up to 1 in 1000 people)

- Seizures (fits)

Unknown: (frequency cannot be estimated from the available data)

- A severe and very low white blood cell count – shown in blood tests
- Haemolytic anaemia (a condition where red blood cells are damaged and reduced in number), which may make you feel tired and turn your skin and eyes yellow
- Swelling of the tongue, face, lips or throat
- Sudden onset of a severe rash with bullseye-like spots or blistering or peeling skin, possibly with a high fever, joint pain, abnormal function of your liver, kidney or lung (these may be signs of more serious medical conditions called toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, acute generalised exanthematous pustulosis, or a condition known as drug reaction with eosinophilia and systemic symptoms (DRESS))
- A positive result from a test called “Coombs” used to identify haemolytic anemia (see above) or reaction of your immune system to Vaborem
- Acute disorientation and confusion (delirium)

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vaborem

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the container. The expiry date refers to the last day of that month.

Do not store above 25 °C.

6. Contents of the pack and other information

What Vaborem contains

- The active substances are meropenem and vaborbactam. Each vial contains 1 g meropenem (as meropenem trihydrate) and 1 g vaborbactam.
- The other ingredient is sodium carbonate.

What Vaborem looks like and contents of the pack

Vaborem is a white to light yellow powder for concentrate for solution for infusion supplied in a vial.

Vaborem is available in packs containing 6 vials.

Marketing Authorisation Holder

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Manufacturer

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This leaflet was last revised in:

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:

<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Vaborem is intended for intravenous (IV) administration, only after reconstitution and dilution. Standard aseptic techniques must be used for solution preparation and administration.

The number of vials used for a single dose will depend on the creatinine clearance (CrCl) of the patient.

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 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 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 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.

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

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 of the SmPC.