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/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
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/min[1]

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

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

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

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

Method of administration

Intravenous use.

Vaborem is administered by intravenous infusion over 3 hours.

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

4.3 Contraindications

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

Hypersensitivity to any carbapenem antibacterial agent.

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

4.4 Special warnings and precautions for use

Hypersensitivity reactions

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

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

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 If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and an alternative treatment should be considered.

Rhabdomyolysis

Rhabdomyolysis has been reported with the use of meropenem, a component of meropenem/vaborbactam. If signs or symptoms of rhabdomyolysis are observed, meropenem/vaborbactam should be discontinued and appropriate therapy initiated.

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).

Drug-induced liver injury (DILI)

Hepatic function should be closely monitored during treatment with meropenem/vaborbactam due to the risk of DILI (see section 4.8). If severe DILI occurs, treatment discontinuation should be considered as clinically appropriate. Meropenem/vaborbactam should be reintroduced only if assessed as essential for treatment.

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).

Clostridioides difficile-associated diarrhoea

Clostridioides 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 *Clostridioides 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 β-lactamases. 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

4.8 Undesirable effects

Summary of the safety profile

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

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

Tabulated list of adverse reactions

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

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

Table 3: Frequency of adverse reactions by system organ class

System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Unknown (cannot be estimated from the available data)
Infections and infestations		*Clostridioides difficile* colitis		

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)
		Vulvovaginal candidiasis Oral candidiasis		
Blood and lymphatic system disorders	Thrombocythaemia	Leucopenia Neutropenia Eosinophilia Thrombocytopenia		Agranulocytosis Haemolytic anaemia
Immune system disorders		Anaphylactic reaction Hypersensitivity		Angioedema
Metabolism and nutrition disorders	Hypokalaemia Hypoglycaemia	Decreased appetite Hyperkalaemia Hyperglycaemia		
Psychiatric disorders		Insomnia Hallucination		Delirium
Nervous system disorders	Headache	Tremor Lethargy Dizziness Paraesthesia	Convulsions	
Vascular disorders	Hypotension	Phlebitis Vascular pain		
Respiratory, thoracic and mediastinal disorders		Bronchospasm		
Gastrointestinal disorders	Diarrhoea Nausea Vomiting	Abdominal distension Abdominal pain		
Hepatobiliary disorders	Alanine aminotransferase	Blood bilirubin increased		

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)
	increased Aspartate aminotransferase increased Blood alkaline phosphatase increased Blood lactate dehydrogenase increased	Drug-induced liver injury[1]		
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)
Musculoskeletal and connective tissue disorders				Rhabdomyolysis [2]
Renal and urinary disorders		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)
		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		

[1] DILI includes hepatitis and liver failure
[2] Observed post-marketing with meropenem, a component of Vaborem

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 Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no experience with overdose of Vaborem.

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

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

Resistance

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

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

Antibacterial activity in combination with other antibacterial agents

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

Susceptibility testing break points

MIC (minimum inhibitory concentration) interpretative criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for meropenem/vaborbactam and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

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 (t½) is 2.30 hours and 2.25 hours for meropenem and vaborbactam, respectively.

Both meropenem and vaborbactam are primarily excreted via the kidneys. Approximately 40-60% of a meropenem dose is excreted unchanged within 24 -

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

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

Linearity/non-linearity

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

Effect of vaborbactam/meropenem on enzymes and transporters

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

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

Special populations

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

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

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

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

5.3 Preclinical safety data

Meropenem

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

Vaborbactam

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate

6.2 Incompatibilities

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

6.3 Shelf life

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

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)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/08/2024

10 DATE OF REVISION OF THE TEXT

27/04/2026