Summary of risk management plan for Vabomere (meropenem/vaborbactam)

This is a summary of the risk management plan (RMP) for Vabomere. The RMP details important risks of Vabomere, how these risks can be minimised, and how more information will be obtained about Vabomere's risks and uncertainties (missing information).

Vabomere's Summary of Product Characteristics (SmPC) and its Package Leaflet give essential information to healthcare professionals and patients on how Vabomere should be used.

This summary of the RMP for Vabomere should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Vabomere's RMP.

I. The medicine and what it is used for

Vabomere is authorised for treatment of the following infections in adults:

- Complicated urinary tract infection (cUTI), including pyelonephritis
- Complicated intra-abdominal infection (cIAI)
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)
- Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Vabomere is also indicated for the treatment of infections due to bacterial organisms in adult patients with limited treatment options (see SmPC for the full indication). It contains meropenem and vaborbactam as the active substances and it is given by intravenous administration.

Further information about the evaluation of Vabomere's benefits can be found in Vabomere's EPAR, including in its plain-language summary, available on the European Medicines Agency website:

http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/004669/human_med_002325.jsp&mid=WC0b01ac058001d124.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Vabomere, together with measures to minimise such risks and the proposed studies for learning more about Vabomere's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

If important information that may affect the safe use of Vabomere is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Vabomere are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Vabomere. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg on the long-term use of the medicine).

Table 1: List of important risks and missing information

Important identified risks	Serious hypersensitivity *Clostridium difficile*-associated diarrhoea Seizures Hepatotoxicity
Important potential risks	Development of resistance to meropenem/vaborbactam
Missing information	Safety profile in patients with severe renal impairment

II.B Summary of important risks

Table 2: Serious hypersensitivity

Important identified risk	
Evidence for linking the risk to the medicine	In Vabomere Phase III studies, one patient experienced a life-threatening infusion-related reaction. No other events of serious hypersensitivity were reported. Although there have not been a lot of hypersensitivity cases with Vabomere, antibiotic treatments are often associated with hypersensitivity reactions. Most emergency department visits for antibiotic-associated adverse events were for allergic reactions [Shehab et al, 2008]. People who are allergic to penicillin may also experience an allergic reaction to Vabomere because they are similar in chemical structure. Hypersensitivity reactions causing rash, itching, and/or hives are the most common and occur in up to 8% of patients who are treated with a penicillin-type antibiotic and up to 3% of patients who receive a cephalosporin-type antibiotic. Anaphylaxis, a more serious type of hypersensitivity reaction, develops in only 0.004% to 0.015% of patients, and death due to this anaphylaxis occurs only in 0.001% to 0.003% of penicillin treatment courses.

Risk factors and risk groups	Patients with known hypersensitivity to carbapenems including meropenem or to other beta-lactams may be at risk of serious hypersensitivity. Hypersensitivity reactions can lead to skin rashes, itching, and, in rare instances, can be serious and life-threatening with need for medical intervention and possible hospitalisation or could potentially cause death.

Risk minimisation measures	Routine risk minimisation measures
	• Routine risk communication:
	  • SmPC Section 4.3
	  • SmPC Section 4.8
	  • PL Section 2
	  • PL Section 4
	• Routine risk minimisation activities recommending specific clinical measures to address the risk:
	  • A recommendation to discontinue treatment if a severe allergic reaction occurs is included in SmPC Section 4.4.

Table 3: *Clostridium difficile*-associated diarrhoea (CDAD)

Important identified risk	
Evidence for linking the risk to the medicine	In Vabomere Phase III studies, one patient experienced a non-serious *Clostridium difficile* colitis after treatment with Vabomere. CDAD is a leading cause of diarrhoea from exposure to bacteria in a hospital. It is a major concern in hospitalized patients. Vabomere will be used to treat hospitalized patients with complicated infections, so the risk of developing CDAD may be higher in these patients.
Risk factors and risk groups	Risk factors include a history of *C. difficile* infection, use of antibiotics in the previous 4 weeks, use of gastric acid suppressors, recent hospitalisation or residence in nursing care, and advanced age are potential risk factors for CDAD [Cioni et al, 2016]. Fluoroquinolones, clindamycin, and third generation cephalosporins have commonly been identified as high-risk antibiotics for the development of CDAD. Treatment with carbapenems (the class of antibiotics that includes meropenem) has also been identified as a risk for developing CDAD [Buckler et al, 2014].

Risk minimisation measures	Routine risk minimisation measures
	• Routine risk communication:
	  • SmPC Section 4.8
	  • PL Section 2
	  • PL Section 4
	• Routine risk minimisation activities recommending specific clinical measures to address the risk:
	  • Recommendations to discontinue treatment with meropenem/vaborbactam, administer specific treatment for *Clostridium difficile*, and not to administer medicinal products that inhibit peristalsis are included in SmPC Section 4.4.

Table 4: Seizures

Important identified risk	
Evidence for linking the risk to the medicine	Beta-lactam antibiotics are known to be associated with seizures. Carbapenem antibiotics (the class of antibiotics that includes meropenem) have been associated with a risk of neurotoxicity, such as seizures [Pestotnik et al, 1993]. Meropenem-associated seizures have also been observed with an incidence of 0.08% [Norrby et al, 1999].
Risk factors and risk groups	Seizures were observed with meropenem mostly in patients with central nervous system (CNS) disorders, bacterial meningitis and/or kidney damage. Risk factors for carbapenem-associated seizure includes underlying CNS disease, history of seizures, kidney damage, and use of high doses of carbapenem antibiotics [Pestotnik et al, 1993]. Drugs given at the same time as Vabomere that are known to increase the risk of seizures may also increase this risk (metronidazole, quinolones, and theophylline). The risk of seizures is also increased in patients treated with the anticonvulsant valproic acid/sodium valproate or valpromide and meropenem at the same time as Vabomere due to an interaction causing a lower blood concentration of the anticonvulsant.

Risk minimisation measures	Routine risk minimisation measures
	• Routine risk communication:
	  • SmPC Section 4.4
	  • SmPC section 4.7
	  • SmPC Section 4.8
	  • PL Section 2
	  • PL Section 4
	• Routine risk minimisation activities recommending specific clinical measures to address the risk:
	  • Warning against concomitant treatment with meropenem and valproic acid, sodium valproate, and valpromide and recommendations that supplemental anticonvulsants are administered if treatment with both therapies are required are included in SmPC Sections 4.4 and 4.5.
	  • Dose adjustment in patients with renal impairment is discussed in SmPC Section 4.2.
	  • A specification of the type of carbapenemases that are not inhibited by vaborbactam is included in the SmPC Section 4.4.

Table 5: Hepatotoxicity

Important identified risk	
Evidence for linking the risk to the medicine	Hepatotoxicity, or liver toxicity, has been reported in patients treated with beta-lactams. Carbapenems have been associated with mild brief liver enzymes elevations. Issues with the bile duct have also been seen [LiverTox: Carbapenems; Serranti et al, 2013]. Safety analyses of patients who were treated with meropenem among other antibiotics for serious bacterial infection in clinical trials showed a drug-induced elevation in liver enzymes caused by meropenem and other similar drugs. However, the rate was low (below 5% of patients), and the elevations were generally not considered clinically significant. Other analyses showed lower rates of abnormal bile duct function tests (1.5% of patients or lower) [Linden, 2007, Norrby et al, 1999].
Risk factors and risk groups	Repetitive administration, female gender, advanced age especially for bile duct disorders, and large total dose have been suggested as risk factors [Quattropani et al, 2001]. Parenteral nutrition and sepsis have also been considered [LiverTox: Carbapenems].

Risk minimisation measures	Routine risk minimisation measures
	• Routine risk communication:
	  • SmPC Section 4.8
	  • PL Section 2
	  • PL Section 4
	Routine risk minimisation activities recommending specific clinical measures to address the risk:
	  • Warning for the hepatic function to be closely monitored during treatment with meropenem/vaborbactam due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis) are included in SmPC Section 4.4.

Table 6: Development of resistance to Vabomere

Important potential risk	
Evidence for linking the risk to the medicine	Development of resistance of bacteria to antibiotics can occur with all antibiotics. It is a serious threat to public health globally because there are few options for treatment of serious infections. It is possible for bacteria to become resistant to Vabomere during treatment of a given patient or to develop resistance overtime after transmission in a community.
Risk factors and risk groups	Using a Vabomere dose below the recommended dose or not giving Vabomere to a patient for a long enough time could increase the risk for development of resistance during Vabomere therapy.

	In the healthcare setting, risk factors that may increase development of antimicrobial resistance are: • Poor hand hygiene of healthcare providers, • Greater severity of illness of hospitalized patients, • Newer devices and procedures in use, • Overuse of antibiotics for prevention of infection rather than for treatment, • Use of Vabomere without complete assessment of whether it will work to treat the infection, • More use in patients who have a very weak immune system, and • An increase of resistant bacteria from the community.
Risk minimisation measures	Routine risk minimisation measures • Routine risk communication: ◦ SmPC Section 5.1 • Routine risk minimisation activities recommending specific clinical measures to address the risk: ◦ A recommendation that the official guidance on appropriate use of antibiotics should be considered is included in SmPC Section 4.1. ◦ A recommendation that meropenem/vaborbactam should be administered only after consulting with a physician with appropriate experience in the management of infectious diseases is included in SmPC Section 4.2. ◦ A specification of the type of carbapenemases that are not inhibited by vaborbactam is included in the SmPC Section 4.4.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Global Microbiology surveillance study to evaluate the worldwide development of resistance to carbapenems including Vabomere. See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 7: Safety profile in patients with severe renal impairment

Missing information	
Risk minimisation measures	Routine risk minimisation measures • Routine risk minimisation activities recommending specific clinical measures to address the risk:

	• Necessary dose adjustments for patients with varying degrees of renal impairment are presented by CrCl in SmPC Section 4.2.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Vabomere.

II.C.2 Other studies in post-authorisation development plan

Global Microbiology surveillance study: Antimicrobial activity of meropenem/vaborbactam tested against a global collection of Gram-negative organisms

Purpose of the study: To monitor the activity of meropenem/vaborbactam at fixed 8 µg/mL and various comparator agents when tested against Gram-negative clinical isolates collected in US, European, Latin American, and Asia-Pacific medical centers from January through December 2017 as part of the SENTRY Antimicrobial Surveillance Program.

This study will enrich the available data for the important potential risk of development of resistance to Vabomere.