Risk Management Plan

Cefepime-Enmetazobactam

Date: 15 Jan 2024

RMP version to be assessed as part of this application:

RMP Version number:	V1.3
Data lock point for this RMP:	31-May-2022
Date of final sign off:	15-Jan-2024
Rationale for submitting an updated RMP:	Response to joint CHMP and PRAC day 195 list of questions (EMEA/H/C/005431/0000)
Summary of significant changes in this RMP	Based on the CHMP recommendation, missing information of “use in immunocompromised population” and “use in paediatric population” have been removed from the list of safety concerns. Part I, Part II (Module SI) and Part VI have been updated to remove the following indication: • Treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options. Part II: Module SI - Epidemiology of the indication(s) and target population(s) has been updated to include details regarding following indication: • Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed under section 4.2 of the SmPC. Data regarding reproductive toxicity has been added under Module II part SVII.3.2 for the missing information of “Use in pregnancy”.

Other RMP versions under evaluation:

RMP Version number:	Not Applicable
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The content of this RMP has been reviewed and approved by the MAH QPPV/Deputy QPPV. The electronic signature is available on file.
Name of EU QPPV/Deputy QPPV: Nowel Redder

LIST OF ABBREVIATIONS

ALT	Alanine aminotransferase
AMR	Antimicrobial resistance
AST	Aspartate aminotransferase
ATS	American Thoracic Society
ATS	American Thoracic Society
COPD	Chronic obstructive pulmonary disease
cUTI	Complicated Urinary Tract Infection
DDI	Drug-Drug interaction
ERS	European Respiratory Society
ESBL	Extended spectrum beta-lactamases
HAP	Hospital-acquired pneumonia
HAUTIs	Healthcare-associated UTIs
MAD	Multiple-ascending dose
MDR	Multi-drugs resistant
MRSA	Methicillin Resistant Staphylococcus aureus
PBP	Penicillin-binding proteins
PK	Pharmacokinetic
PN	Pyelonephritis
RMP	Risk Management Plan
SAD	Single-ascending dose
US CDC	United States Centers for Disease Control and Prevention
UTI	Urinary tract infection
VAP	Ventilator-Associated Pneumonia

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Cefepime- Enmetazobactam
Pharmacotherapeutic group(s) (ATC Code)	Antibacterial for systemic use, other beta-lactam antibacterial, fourth generation cephalosporins ATC code: J01DE51
Marketing Authorisation Holder	Advanz Pharma Group
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	EXBLIFEP 2 g/0.5 g powder for concentrate for solution for infusion
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	*Chemical class*: Cefepime is a cephalosporin (fourth generation) in the beta-lactam class of antibiotics. Enmetazobactam is a penicillanic acid sulfone β-lactamase inhibitor with potent activity against β-lactamases.
	Summary of mode of action: Cefepime exerts bactericidal activity by inhibiting peptidoglycan cell wall synthesis as a result of binding to and inhibition of penicillin-binding proteins (PBPs). Cefepime is generally stable to hydrolysis by class C AmpC and class D OXA-48 enzymes. Enmetazobactam is a penicillanic acid sulfone beta-lactamase inhibitor structurally related to penicillin. Enmetazobactam binds to β-lactamases and prevents the hydrolysis of cefepime. It is active against class A ESBLs. Enmetazobactam does not reliably inhibit class A carbapenemase KPC and does not inhibit class B, class C or class D beta-lactamases.
	Important information about its composition: Each vial contains cefepime dihydrochloride monohydrate equivalent to 2 g cefepime and 0.5 g of enmetazobactam.
Hyperlink to the Product Information	Module 1.3.1 of Dossier
Indication(s) in the EEA	Current (if applicable): Exblifep is indicated for the treatment of the following infections in adults:

	• Complicated urinary tract infections (cUTI), including pyelonephritis • 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.
	Proposed (if applicable): NA
Dosage in the EEA	Current (if applicable): For complicated urinary tract infections (cUTI), including pyelonephritis, the recommended dose for patients with normal renal function is 2 g/0.5 g cefepime/enmetazobactam every 8 hours administered as an intravenous infusion over 2 hours. In patients with augmented renal clearance (eGFR > 150 mL/min) prolongation of the infusion to 4 hours is recommended. For hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP), the recommended dose for patients with normal renal function is 2 g/0.5 g cefepime/enmetazobactam every 8 hours administered as an intravenous infusion over 4 hours. The usual duration of treatment is 7 to 10 days. In general, administration should not be not less than 7 days and not longer than 14 days. In patients with bacteraemia treatment up to 14 days may be required. Refer section 4.2 of the SmPC for complete details on posology. <u>Method of administration</u>: Cefepime/enmetazobactam is administered via intravenous infusion
	Proposed: NA
Pharmaceutical form(s) and strengths	Current (if applicable): Powder for concentrate for solution for infusion. Each vial contains cefepime dihydrochloride monohydrate equivalent to 2 g cefepime and 0.5 g of enmetazobactam.
	Proposed: NA
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Complicated Urinary Tract Infection (cUTI) including pyelonephritis (PN)

Incidence: Epidemiological data of cUTI in the EU are limited. In the United States, a large retrospective and longitudinal study using Pharmetrics database identified 543 502 patients with a cUTI diagnosis resulting in an estimated cUTI incidence rate of 4.9 cases per 1000 person years and weighted count of 2 882 195 cUTI cases in 2017 for US corresponding to an estimated proportion of adult persons in US who experienced a cUTI in 2017 of 1.14%.[1] Acute pyelonephritis was reported as a subset of cUTI with an incidence of 250 000 cases in the US annually.[2]

Prevalence: Infectious complications following urological procedures are a major issue, particularly in the context of increasing antimicrobial resistance. Over 4 million patients acquire healthcare-associated infections in the European Union every year, 20−30% of which are considered preventable. Healthcare-associated UTIs (HAUTIs) represent the largest subtype among all healthcare-associated infections. The prevalence of HAUTIs assessed in regional studies ranges from 12.9% in the US and 19.6% in Europe, to up to 24% in developing countries.[3]

The large, ongoing Global Prevalence Study on Infections in Urology (GPIU study) aimed to gain a global perspective on HAUTIs revealed that between 2003 and 2010, 19,756 patients were assessed, 9.4% of whom were diagnosed with a HAUTI (70.4% of whom were female).[3]

Age, gender:

The study conducted by Carreno et al showed that the incidence rate of cUTI is increasing with age but differently for male and female. The incidence rate is higher for women than men for the strata below 55 years aged, similar for the strata 55–64 and lower for strata above 64 years age. For female patients, the largest increase in incidence rate was between the 55 to 64 and the ≥ 65 years age groups. For men, the risk increased exponentially throughout the ages to reach 3% for men > 65 years old.[1]

Risk factors for the disease:

A complicated UTI is an infection associated with a condition, such as a structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease, which increase the risk of a more serious outcome than expected from UTI in individuals without identified risk factor or of failing therapy.[4] Guidelines on urological infections from European Association of Urology listed risk factors for UTIs with or without risk of more severe outcomes as mentioned below (Table 1 Part II Module SI).[4]

Table Part II: Module SI: Host risk factors in UTI

Category of risk factor	Examples of risk factor
No known/associated RF	• Healthy premenopausal women
Recurrent UTI RF, but no risk of severe outcome	• Sexual behaviour and contraceptive devices • Hormonal deficiency in post menopause • Secretory type of certain blood groups • Controlled diabetes mellitus

Extra-urogenital RF, with risk of more severe outcome	• Pregnancy • Male gender • Badly controlled diabetes mellitus • Relevant immunosuppression* • Connective tissue diseases* • Prematurity, new-born
Nephropathic disease, with risk of more severe outcome	• Relevant renal insufficiency* • Polycystic nephropathy
Urological RF, with risk of more severe outcome, which can be resolved during therapy	• Ureteral obstruction (i.e. stone, stricture) • Transient short-term urinary tract catheter • Asymptomatic Bacteriuria** • Controlled neurogenic bladder dysfunction • Urological surgery
Permanent urinary **C**atheter and non-resolvable urological RF, with risk of more severe outcome	• Long-term urinary tract catheter treatment • Non-resolvable urinary obstruction • Badly controlled neurogenic bladder

RF = risk factor; * = not well defined; ** = usually in combination with other RF (i.e., pregnancy, urological intervention)

The main existing treatment options:

Guidelines recommend treating cUTI with a 7–14-day course of antibiotics. In cases of severe UTI, empiric intravenous antibiotic therapy is mostly advised, with pathogen-directed adjustments to be made as soon as antibiotic susceptibility patterns are known. Appropriate empirical treatment options that cover most probable causing pathogens are therefore critical, especially in severe infections and vulnerable patients. The successful treatment of a complicated UTI always combines effective antimicrobial therapy, optimal management of the underlying urological abnormalities or other diseases, and sufficient life-supporting measures. Recommended options for initial empirical treatment depend on local resistance patterns, initial therapy failure and case severity. It includes fluoroquinolones, aminopenicillins plus a β-lactamase inhibitor, cephalosporines, piperacillin plus a β-lactamases inhibitor and carbapenems.[4]

The growing of antimicrobial resistance (AMR) is now a major concern worldwide, limiting the treatment options for many infectious diseases including cUTI. It was estimated that *Escherichia coli* and *Klebsiella pneumoniae* each are responsible for around 200 000 deaths attributable to AMR in 2019.[5]

There is a high and growing prevalence globally of Extended Spectrum β-lactamases (ESBL). Hospital cohorts in US showed an increase of ESBL infections by 53% (from 37.6 to 57.2 cases per 10000 hospitalizations) driven by the incidence of community onset cases.[6]

In 2017, US CDC (United States Centres for Disease Control and Prevention) estimated 197 000 cases due to ESBL producing enterobacterial with 9 100 attributable deaths.[7]

The ESBLs mediate resistance to third generation (3GC) cephalosporins.

Third-generation cephalosporin-resistant and carbapenem-resistant Enterobacterial appear in the highest category on WHO's list of priority pathogens for research and development of new antibiotics.[8]

The high and growing prevalence of (ESBL) enzymes has limited the antimicrobial arsenal available for both empiric and pathogen-directed treatment of cUTI. The high rates of co-resistance to fluoroquinolones, aminoglycosides and trimethoprim-sulfamethoxazole, are further limiting treatment options.[9]

Natural history of the indicated condition in the cUTI including PN population, including mortality and morbidity:

cUTI including PN are infections potentially life threatening with the risk of progress to a severe sepsis, multi-organ involvement and septic shock. Mortality rates vary significantly between studies (0.4 % to 33%). A large retrospective cohort study showed a mortality rate of 0.4% in US.[10] In another study the mortality rate was of 8.7 %, mostly catheter associated (Eliakim-Raz N, 2017) while a study in elderly patients showed a mortality rate of 30.8%.[11]

Risk factors for treatment failure in RESCUING study were ICU, septic shock, corticosteroid treatment, bedridden, older age, metastatic cancer, and catheter associated UTI.[12]

Important co-morbidities:

Important co-morbidities are especially those more frequent in elderly and those related to immunosenescence.

Hospital-acquired pneumonia (HAP), including Ventilator-Associated Pneumonia (VAP)

Incidence:

Nosocomial pneumonia accounted for 22% of all hospital infections in the United States.[13] It is the second most common infection in hospitalized patients, and the most common infection in the intensive care unit responsible for one-fourth of all intensive care unit (ICU) infections[14,15] with an incidence range from 5 to more than 20 cases per 1000 hospital admissions (ATS, 2005).

In US, about 10% of patients on mechanical ventilation develop VAP[16] and the incidence of VAP ranges from 2 to 16 episodes per 1,000 ventilator-days.[17] The estimated risk of VAP is 1.5% per day and decreases to less than 0.5% per day after the 14th day of mechanical ventilation.[18]

Prevalence:

Data relevant to European population not available.

Age, gender:

Nosocomial pneumonia is most common in elderly patients; however, patients of any age may be affected. Risk of HAP in older patients was estimated to 0.3% in a UK study.[19]

Data regarding gender as risk factor of HAP are contradictory.[20]

Risk factors for the disease:

Patient related identified factors are acute or chronic severe disease, coma, malnutrition, prolonged hospital length of stay, hypotension, metabolic acidosis, smoking and comorbidities especially of the

central nervous system as abnormal swallowing function, but also chronic obstructive pulmonary disease (COPD), respiratory insufficiency, diabetes, mellitus, alcoholism, chronic renal failure.[21]

Amongst risk factors related to infection prevention, are deficient hand hygiene or inappropriate care of respiratory support devices.[21]

Factors related to procedures: administration of sedatives, corticosteroids and other immunosuppressants, prolonged surgical procedures (especially at thoracic or abdominal level) and inappropriate antibiotic treatment are the most recognized factors[22,23,24], treatment with gastric acid-modifying drugs[25], endotracheal intubation, micro aspiration around endotracheal tube, prolonged duration of ventilation, secretions pooled above endotracheal tube.[22,26]

High incidence has been reported in trauma and brain injury patients.[27]

The main existing treatment options:

American Thoracic Society (ATS) guidelines suggest that patients with suspected HAP (non-VAP) be treated according to the results of microbiologic studies performed on respiratory samples obtained noninvasively, rather than being treated empirically. ATS also recommends in patients with suspected VAP, to include a coverage for *S. aureus*, *Pseudomonas aeruginosa*, and other Gram-negative bacilli in all empiric regimens. Short-course antibiotic therapy (7 days) is also recommended for most patients with HAP or VAP independent of microbial aetiology, as well as antibiotic de-escalation.[22]

European Respiratory Society (ERS) guidelines recommend initial empiric combination therapy for high-risk HAP/VAP patients to cover Gram negative bacteria and include antibiotic coverage for Methicillin Resistant *Staphylococcus aureus* (MRSA) in those patients at risk. ERS also recommends broad-spectrum empiric antibiotic therapy targeting *Pseudomonas aeruginosa* and ESBL-producing organisms, in settings with high prevalence of *Acinetobacter spp.*, in patients with suspected early onset HAP/VAP who are in septic shock, in patients who are in hospitals with a high background rate of resistant pathogens present in local microbiologic data, and in patients with other (non-classic) risk factors for multi-drugs resistant (MDR) pathogens.[28]

Natural history of the indicated condition in HAP/ VAP population, including mortality and morbidity:

Overall, HAP mortality rate in a prospective multi-centre study in China was of 16. 6%[29], and attributable mortality resulting from ventilator associated pneumonia approximately 10% from a meta-analysis.[30]

In a UK study in older patients the hospital death rate was 29% for patients with HAP versus 8% for those not having HAP.[19]

The overall attributable mortality of VAP was estimated in 13%, with higher mortality rates in surgical patients and those with mid-range severity scores at admission.[31]

Important co-morbidities:

Important comorbidity is especially those related to immunoscenescence and those more frequent in elderly.

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

Incidence and Prevalence

A retrospective cohort study assessing prospectively collected data of all clinically significant bacteraemia's between 1991 and 2020 revealed that the incidence of bacteraemia increased to 205.1/100,000 population in 2016–2020 vs 43.8 in 1991–1995 (RR 4.68, 95% CI 4.23–5.17). Bloodstream infections (BSI) sources such as pneumonia (12.2% vs 9.9%), endocarditis (5.5% vs 3.5%) and urinary catheterisation (9.3%

vs 2.8%) was more common in males and urinary aetiology without catheter was more common in females (27.9% vs 23.4%, $p < 0.001$). *E. coli, S. aureus* and *Streptococcus pneumoniae* were the most common microorganisms. The isolated microorganism varied according to bacteraemia source. *E. coli* was more commonly associated with urinary (55%) and biliary tract (25.3%); *Proteus mirabilis* in urinary tract (74.4%); *Klebsiella spp* in biliary (40.6%) and urinary tract (35.1%); *S. aureus* in endocarditis (21.4%), skin and soft tissue (15.1%) and pneumonia (14.2%); *Enterococcus spp*. in urinary tract (28.8%) and endocarditis (28.8%); *S. pneumoniae* in pneumonia (83%) or meningitis source (9.4%). The incidence of hospital-acquired bacteraemia increased (RR 2016–2020 vs 1991–1995: 3, 95% CI 2.6–3.5), especially that of vascular catheter (RR 2016–2020 vs 1991–1995: 4, 95% CI 3.1–5.2) and urinary tract source (RR 2016–2020 vs 1991–1995: 3.7, 95% CI 2.5–5.6).[32]

Age, gender:

A total of 6777 episodes of clinically significant bacteraemia's were identified between 1991 and 2020. Out of the total, 4043 (59.7%) occurred in males, mean age 66.5 ± 18.2 (range 0–99 years), 39.4% ≥ 75 years old.[32]

The evolution of incidence and patient characteristics are shown below.[32]

Characteristics	**Years**					
	1991–1995	1996–2000	2001–2005	2006–2010	2011–2015	2016–2020
No episodes	476	676	790	1175	1705	1955
Male n(%)	264 (55.5)	404 (59.8)	462 (58.5)	727 (61.9)	1010 (59.2)	1176 (60.2)
Age, mean ± SD	62.1 ± 19.6	57.1 ± 23.9	63.5 ± 18.9	65.5 ± 18.2	68.7 ± 16.3	70.6 ± 15

In a retrospective review of positive blood culture results of 181 cases of bacteraemia in 177 febrile infants aged 90 days or younger, E coli was the most common causative pathogen (42%), followed by group B Streptococcus (23%). Streptococcus pneumoniae was more common in older infants.[33]

Pneumococcal bacteraemia is observed in children of all ages; however, children aged 6 months to 2 years are at an increased risk. The prevalence of pneumococcal meningitis peaks in infants aged 3-5 months. Meningococcal bacteraemia occurs most frequently in infants aged 3-12 months; the highest risk of meningococcal meningitis is in infants aged 3-5 months. The risk of Salmonella bacteraemia is greatest in infants younger than 1 year, especially in those younger than 2 months.[33]

A seasonal variation in febrile children presenting for evaluation is recognized. The peak is from late fall to early spring in children of all ages and is likely because of respiratory and GI viral infections. Another peak occurs during the summer in infants younger than 3 months and is likely due to enteroviral infections and thermoregulation during hot weather. However, most studies do not specifically address seasonal variation associated with bacteraemia.[33]

Risk factors for the disease:

- Children younger than 1 year old
- Adults older than 65 years old
- Weakened immune system
- Underlying health conditions like diabetes, kidney disease, or cancer
- Underlying infections (UTI, pneumonia etc.)

- Individuals who have recently undergone a tooth extraction, medical procedure, or surgery or who have recently been hospitalized

The main existing treatment options:

Antibiotics

In patients with suspected bacteraemia, empiric intravenous antibiotics are given after appropriate cultures of potential sources and blood are obtained. Early treatment of bacteraemia with an appropriate antimicrobial regimen appears to improve survival.[34]

Continuing therapy involves adjusting antibiotics according to the results of culture and susceptibility testing, draining any abscesses, and usually removing any internal devices that are the suspected source of bacteria. Once source control is achieved and clinical improvement is observed, therapy can be completed with appropriate oral antibiotics.[34]

Natural history of the indicated condition including mortality and morbidity:

The natural history, morbidity, and mortality associated with bacteraemia alone are not clearly understood. In prospective studies of occult bacteraemia, although many children were initially observed untreated, all were given antibiotics once blood culture findings became positive for known bacterial pathogens.[33]

In studies performed before the introduction of the *Haemophilus influenzae* type b (Hib) conjugate vaccine, children with untreated bacteraemia had an 18-21% risk of developing persistent bacteraemia and a 2-15% risk of developing important focal infections such as meningitis.[33]

Because widespread use of the Hib vaccine has virtually eliminated invasive Hib disease in the developed world, recent reviews, analyses, and studies have focused on invasive *S pneumoniae* disease. Children with occult pneumococcal bacteraemia have a 6-17% risk of persistent bacteraemia, a 2-5.8% risk of meningitis, and a 6-10% risk of other focal complications.[33]

Of all focal infections that develop because of pneumococcal bacteraemia, pneumococcal meningitis carries the highest risk for significant morbidity and mortality, including a 25-30% risk of neurologic sequelae such as deafness, mental retardation, seizures, and paralysis. The mortality rate of pneumococcal meningitis is 6.3-15%, and the overall mortality rate of pneumococcal bacteraemia is 0.8%.[33]

Neisseria meningitidis also causes bacteraemia in infants and young children. Although the prevalence of meningococcal bacteraemia is much lower than that of pneumococcal disease, the morbidity and mortality rates are much greater. Children with meningococcal bacteraemia have a 42-50% risk of developing meningitis; a 50% risk of developing serious bacterial infection such as septic shock, pneumonia, and neurologic changes; a 3% risk of developing extremity necrosis; and an overall mortality rate of 4%.[33]

When untreated, *Salmonella* bacteraemia carries a 50% risk of persistent bacteraemia and can cause meningitis, sepsis, and death in infants younger than 3 months or in persons who are debilitated or immunocompromised. However, in previously healthy children aged 3-36 months, the risk of meningitis or serious bacterial infection following *Salmonella* bacteraemia is low.[33]

Important co-morbidities:

- Diabetes Mellitus
- Hypertension
- Congestive Heart Failure

- Ischemic Heart Disease
- Malignancy
- End-Stage Renal Disease (ESRD)
- Chronic Obstructive Pulmonary Disease (COPD)

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage[35]:

Toxicity

- The non-clinical experience with enmetazobactam did not reveal any noteworthy safety issues, nor was there evidence of cardiac toxicity, mutagenicity, or genotoxicity reproductive, local or developmental toxicity and demonstrated no evidence that would indicate any unacceptable risk for intravenous administration of enmetazobactam. No teratogenicity was evidenced at any dose.
- Toxicology studies characterized two potentially clinically relevant toxicities of enmetazobactam to the liver and kidney. Repeated dose toxicity studies of enmetazobactam in rats (28 days), Beagle dogs (13 weeks) and juvenile rats (14 days) identified the liver as the target organ for toxicity. This finding is potentially relevant for human risk assessment of cefepime – enmetazobactam treatment**.**
- Carcinogenicity studies of enmetazobactam are not foreseen, based on the intended short-term duration of therapy (7 to 14 days for most patients) and because test results showed no potential for genotoxicity.

Safety pharmacology

- The *in vitro* and *in vivo* safety pharmacology studies of enmetazobactam did not reveal any significant effect on respiratory function, central and peripheral nervous system and cardiovascular parameters.
- Research for biomarkers of liver injury indicated a mechanism of action not involving primary mitochondrial damage or an immune response with a dose dependent increase in fragmented Keratin 18 indicating in apoptotic and not necrotic balance of cell death. An analysis of the observed liver enzyme elevations with DILIsym® Software Platform to estimate the magnitude of liver compromise observed in multi dose phase I trial with enmetazobactam indicated that the safety margin of enmetazobactam at cumulative doses below 50 g (dosed over 14 days) appeared to be high with an amount of hepatocyte loss that likely occurred with enmetazobactam at doses closest to the therapeutic levels would be practically and directly undetectable and clinically benign with respect to liver function. Furthermore, the amount of hepatocyte loss that likely occurred for all previously administered cumulative doses of enmetazobactam (20 g to 106 g dosed over 14 days) would be without detectable or significant loss of liver function and clinically benign.

Other toxicity-related information or data:

Not applicable.

Part II: Module SIII - Clinical trial exposure

There were six clinical studies in the Enmetazobactam clinical development program which examined the pharmacokinetic properties of either cefepime and/or Enmetazobactam[36].

Study No.	Study Design	Treatment groups
AT-101 SAD/DDI	Phase 1, Randomized, double-blind, placebo-controlled, inpatient sequential, Single-ascending dose (SAD)	**SAD** Cohort 1: enmetazobactam 160 mg IV over 30 min Cohort 2: enmetazobactam 600 mg IV over 30 min Cohort 3: enmetazobactam 1 g IV over 30 min in the morning Cohort 4: enmetazobactam g IV over 30 min Cohort 5: enmetazobactam 4 g IV over 30 min Cohort 6: enmetazobactam 1 g IV over 30 min q6h Cohort 7: enmetazobactam 2 g IV over 30 min q6h **Drug-Drug interaction (DDI)** Sequence 1: a) piperacillin 4 g; b) enmetazobactam 2 g IV; c) enmetazobactam 2 g + piperacillin 4 g IV; d) cefepime 2 g IV e) enmetazobactam 2 g + cefepime 2 g IV Sequence 2: a) cefepime 2 g IV; b) piperacillin 4 g IV; c) enmetazobactam 2 g + cefepime 2 g IV; d) enmetazobactam 2 g IV e) enmetazobactam 2 g + piperacillin 4 g IV
AT-101 MAD	Phase 1, Randomized, double-blind, placebo-controlled, multiple-ascending dose (MAD)	MAD Solo Part enmetazobactam 1 g IV over 30 min q6h for 14 days or enmetazobactam 2 g IV, over 30 min q6h for 14 days MAD Combo Part • cefepime 1 g + enmetazobactam 500 mg IV over 30 min q8h for 14 days • piperacillin 3 g + enmetazobactam 500 mg IV over 30 min q6h for 14 days Continuous Infusion Part enmetazobactam 4 g/day IV as a continuous infusion for 14 days

AT-102	Phase 1, Multicentre, open-label, Pharmacokinetic (PK), safety, single dose study in combination with cefepime to evaluate the pharmacokinetic parameters of a single dose of enmetazobactam in combination with cefepime in subjects with RI compared with subjects with normal renal function	Normal renal function and mild and moderate RI: cefepime 1 g + enmetazobactam 500 mg IV over 2 hours Severe RI and ESRD: cefepime 500 mg + enmetazobactam 250 mg IV over 2 hours
AT-103	Phase 1, Open-label, single-centre study to measure and compare the concentration of enmetazobactam and cefepime in ELF and plasma	cefepime 2000 + enmetazobactam 1000 mg IV over 2 hours q8h for 72 h
AT-104	Phase 1, Open-label, single-dose, pharmacokinetic, single-centre study to assess the mass balance, PK and routes of elimination of enmetazobactam and to determine metabolic profiles	[^{14}C]-labelled enmetazobactam 500 mg IV over 2 hours
AT-201	Phase 2, Randomized, double-blind, multicentre, 2 cohort study to determine the optimal cefepime + enmetazobactam combination dose and to assess the PTA and the effect of treatment on liver enzymes	cefepime 1 g + enmetazobactam 500 mg IV over 2 hours q8h for 7-10 days cefepime 2 g + enmetazobactam 750 mg IV over 2 hours q8h for 7-10 days
AT-301	Phase 3, Randomized, double-blind, active-controlled, multicentre, noninferiority study to assess the efficacy of cefepime-enmetazobactam compared with piperacillin-tazobactam in the treatment of cUTI, including AP	cefepime 2 g + enmetazobactam 500 mg IV over 2 hours q8h for 7-14 days[a] piperacillin 4 g + tazobactam 0.5 g IV over 2 hours q8h for 7-14 days[b]

a. BAL was performed only once per subject, with samples collected for 5 of the 20 subjects at each time point

b. Up to 14 days in subjects with a positive blood culture at baseline.

Table SIII.1: Duration of exposure to cefepime-enmetazobactam

Only 2 trials were performed in patients: both in cUTI (AT-201 and AT-301))

Cumulative for all indications (person time)		
Duration of exposure	Patients	Person day
<7 d	25	98
≥7 d < 10 d	487	3853
≥10 d <14 d	24	269
≥14d ≤ 15 d	10	148
Total person time	4368	

Table SIII.2: Age group and gender

Age group	Patients		Person day	
	M	F	M	F
18 to 64 years	117	214	938	1729
Elderly people	125	90	996	705
65-74 years	80	54	641	426
75-84 years	39	31	307	241
85 + years	6	5	48	38
Total	242	304	1934	2434

Table SIII.3: Dose

Dose of exposure	Patients	Person day
CEFEPIME 1g / ENMETAZOBACTAM 500mg	15	134
CEFEPIME 2g / ENMETAZOBACTAM 500mg	516	4117
CEFEPIME 2g / ENMETAZOBACTAM 750mg	15	117
Total	546	4368

Table SIII.4: Ethnic origin

Ethnic origin	Patients	Person day
Hispanic or Latino	40	305
Non hispanic or latino	505	4059
Not reported	1	4
Total	*546*	4368

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Immunocompromised patients (Exclusion criteria as per AT-201 and AT-301)

Reason for exclusion: The exclusion criteria regarding immunocompromised patients was based on cefepime SmPC section 4.1 "In patients at high risk of severe infections (*e.g.*, patients with recent bone marrow transplantation, hypotension at presentation, underlying haematological malignancy, or severe or prolonged neutropenia), antimicrobial monotherapy may be inappropriate. No sufficient data exist to support the efficacy of cefepime monotherapy in such patients. A combination therapy with an aminoglycoside or glycopeptide antibiotic may be advisable, taking into consideration the patient's individual risk profile".

Is it considered to be included as missing information?

Answer: No

Rationale:

Although there is no safety data in the immunocompromised population it is not expected that the safety profile, when used in this population, will differ significantly compared with when used in non-immunocompromised patients. Concerns related to lack of efficacy in this population may be relevant but is not expected to be reflected amongst the safety concerns in this RMP. Therefore, use in immunocompromised population is not considered as a safety concern/missing information.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	

<table>
<tr>
<td>Patients with relevant comorbidities:
• Patients with hepatic impairment
• Patients with renal impairment
• Patients with cardiovascular impairment
• Immunocompromised patients
• Patients with a disease severity different from inclusion criteria in clinical trials</td>
<td><not included in the clinical development program>
Except for patients with renal impairment in AT-201 and AT-301
AT-301
<table>
<tr><th>eGFR</th><th>Patients</th><th>Person-Days</th></tr>
<tr><td>< 30 mL/min/1.73 m2</td><td>3</td><td>17</td></tr>
<tr><td>30-59 mL/min/1.73 m2</td><td>99</td><td>817</td></tr>
<tr><td>60-89 mL/min/1.73 m2</td><td>280</td><td>2239</td></tr>
<tr><td>Total</td><td>382</td><td>3073</td></tr>
</table>
AT-201
<table>
<tr><th>Creatinine clearance</th><th>Patients</th><th>Person-Days</th></tr>
<tr><td>< 30 mL/min</td><td>0</td><td>0</td></tr>
<tr><td>30-59 mL/min</td><td>1</td><td>4</td></tr>
<tr><td>60-89 mL/min</td><td>11</td><td>87</td></tr>
<tr><td>Total</td><td>12</td><td>91</td></tr>
</table>
</td>
</tr>
<tr><td>Population with relevant different ethnic origin</td><td>Not included in the clinical development program</td></tr>
<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>Not included in the clinical development program</td></tr>
<tr><td>Other
.</td><td>Not included in the clinical development program</td></tr>
</table>

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

List of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• Use in pregnant women • Use in lactating women

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP

- Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

  None

- Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

  None

- Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (*e.g.;* actions being part of standard clinical practice in each EU Member state where the product is authorised):

  List of risk:

Clostridium difficile-associated diarrhoea.

  - Neurotoxicity
  - Hypersensitivity
  - Renal Toxicity
  - Use in patients with renal impairment

  These risks have been well identified with cefepime alone and there is no signal to suspect an increase in frequency or severity due to the combination of cefepime with enmetazobactam.

- Known risks that do not impact the risk-benefit profile

  - Potential risk of liver toxicity

  A potential risk of Alanine aminotransferase / Aspartate aminotransferase (ALT / AST) asymptomatic, transient increase not associated with a bilirubin increase, dose dependent was detected in a 14 days multi dose phase I trial in healthy volunteers for daily dose of enmetazobactam of 4 and 8 g, significantly above the therapeutic dose of 1.5 g daily. This liver toxicity signal was not found in the phase II (AT-201) and phase III (AT-301) in cUTI patients with daily enmetazobactam dose of 2.25 g and 1.5 g. No case fulfilling Hy's Law criteria occurred in the clinical development programme.
  The risk factor is the non-respect of dose adjustment in patient with renal function impairment leading to an overdosage in these patients. The dose adjustment in patients with renal impairment highlighted in SmPC Section 4.2 will address this risk.

- Other reasons for considering the risks not important:
  - Development of resistance to cefepime- enmetazobactam

  Development of antibiotic resistance can occur with all antibiotics. No AE of bacterial resistance development was reported from the studies in the cefepime- enmetazobactam development programme. In the phase 3 study, no patient infected with a susceptible pathogen at baseline was found to have a resistant pathogen at the last follow up visit after 7 to 14 days of treatment with cefepime- enmetazobactam.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk:

None

Important Potential Risk:

None

Missing information:

- Use in pregnant women
- Use in lactating women

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not Applicable

SVII.3.2. Presentation of the missing information

Missing Information – Use in pregnant women	
Evidence source(s)	Population in need of further characterisation: There are no data from the use of cefepime- enmetazobactam in pregnant women. Animal studies indicate reproductive toxicity at relevant clinical exposure of enmetazobactam but no signs of teratogenicity. Enmetazobactam should only be used during pregnancy when clearly indicated and only if the benefit for the mother outweighs the risk for the child. In reproductive toxicity of enmetazobactam in rat and rabbit, delayed skeletal ossification (localised to the skull) were recorded in both rat and rabbit. Increased post-implantation loss, lower mean foetal weight, and skeletal changes (sternum with fused sternebrae) were recorded in rabbit. These effects were observed together with maternal toxicity and at clinically relevant doses. Thus, NOAEL for rat is 250 mg/kg/day and for rabbit 50

Missing Information – Use in pregnant women	
	mg/kg/day with a margin to the exposure at maximum recommended human dose of 1.14-fold and 1.10-fold, respectively. In a peri-postnatal study on rat, lower pup weight, a slight delay in the pre-weaning development and reduced motor activity for a few males during the maturation phase were observed in the F1 generation. No abnormalities were seen in pups culled on Day 4 post-partum, with exception of hindlimb lesions (rotation of paw and/or swollen paw), which were recorded in 2 pups from different litters in the F2 generation at 500 mg/kg/day. NOAEL for the F1 generation were 125 mg/kg/day and for maternal toxicity and F2 development 250 mg/kg/day, with a margin to the exposure at maximum recommended human dose of 0.68-fold and 1.14-fold, respectively.[37]

Missing Information – Use in lactating women	
Evidence source(s)	Population in need of further characterisation: Physico-chemical data suggest excretion of cefepime- enmetazobactam in human milk and cefepime-enmetazobactam has been shown to be excreted in milk from rats. A risk to the new-borns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from cefepime- enmetazobactam therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.[37]

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns*	
Important identified risks	• None
Important potential risks	• None
Missing information	• Use in pregnant women • Use in lactating women

**The summary of safety concerns is based on cefepime- enmetazobactam 2 g/0.5 g powder for concentrate for solution for infusion's product information and current scientific knowledge.*

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activity is planned.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine Risk Minimisation Measures

Safety concern	Routine risk minimisation activities
Missing Information	
Use in pregnant women	**Routine risk communication:** SmPC section 4.6 PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations on cautious use of cefepime-enmetazobactam during pregnancy are included in SmPC section 4.6. Advice in PL section 2 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to medical prescription.
Use in lactating women	**Routine risk communication:** SmPC section 4.6 PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Advise to either discontinue breast-feeding or to discontinue/abstain from cefepime-enmetazobactam therapy in lactating females are included in SmPC section 4.6. Advice in PL section 2 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to medical prescription.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product

V.3 Summary of risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing Information		
Use in pregnant women	Routine risk minimisation measures: Recommendations on cautious use of cefepime-enmetazobactam during pregnancy are included in SmPC section 4.6. Advice in PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in lactating women	Routine risk minimisation measures: Advise to either discontinue breast-feeding or to discontinue/abstain from cefepime-enmetazobactam therapy in lactating females are included in SmPC section 4.6. Advice in PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

This is a summary of the risk management plan (RMP) for Exblifep 2 g/0.5 g powder for concentrate for solution for infusion. The RMP details important risks of Exblifep and how these risks can be minimised.

Exblifep's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how cefepime-enmetazobactam should be used.

This summary of the RMP for Exblifep should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 Exblifep's RMP.

I. The medicine and what it is used for

Exblifep is authorised for the treatment of:

- Complicated urinary tract infections, including pyelonephritis.
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)

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

It contains cefepime-enmetazobactam as the active substance and it is administered as intravenous infusion.

Further information about the evaluation of Exblifep's benefits can be found in Exblifep's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

Important risks of Exblifep together with measures to minimise such risks and the proposed studies for learning more about Exblifep'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.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

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

II.A List of important risks and missing information

Important risks of Exblifep 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 Exblifep. 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 (e.g., on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• Use in pregnant women • Use in lactating women

II.B Summary of important risks

Important Identified Risk: None	
Important Potential Risk: None	
Missing Information- Use in pregnant women	
Risk minimisation measures	Routine risk minimisation measures: • Recommendations on cautious use of cefepime- enmetazobactam during pregnancy are included in SmPC section 4.6. • Advice in PL section 2 Additional risk minimisation measures: None
Missing Information- Use in lactating women	
Risk minimisation measures	Routine risk minimisation measures: • Advise to either discontinue breast-feeding or to discontinue/abstain from cefepime- enmetazobactam therapy in lactating females are included in SmPC section 4.6 • Advice in PL section 2 Additional risk minimisation measures: None

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 cefepime- enmetazobactam.

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

There are no studies required for cefepime- enmetazobactam.

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable