ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

EXBLIFEP 2 g/0.5 g powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cefepime dihydrochloride monohydrate equivalent to 2 g cefepime and 0.5 g of enmetazobactam.

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 yellowish powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EXBLIFEP is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1):

- 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.

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

4.2 Posology and method of administration

Posology

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 (see section 5.2).

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 less than 7 days and not longer than 14 days. In patients with bacteraemia treatment up to 14 days may be required.

Special populations

Elderly

No dose adjustment is necessary for the elderly based on age alone (see section 5.2).

Renal impairment

Dose adjustment is recommended in patients with renal impairment who have an absolute estimated glomerular filtration rate (eGFR) less than 60 mL/min (see section 5.2). The recommended dose in patients with varying degrees of renal function is presented in Table 1.

Patients receiving continuous renal replacement therapy (CRRT) need a higher dose than patients on haemodialysis. For patients receiving continuous renal replacement therapy, the dose should be adjusted guided by the CRRT clearance (CL_{CRRT} in mL/min).

For patients with changing renal function, serum creatinine concentrations and eGFR should be monitored at least daily and the dose of EXBLIFEP adjusted accordingly.

For patients with Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP), infusion time should be 4 hours regardless of the renal impairment status.

Table 1: Recommended dose of EXBLIFEP in patients with renal impairment

Absolute eGFR (mL/min)	**Recommended dose regimen for EXBLIFEP (cefepime and enmetazobactam)**	**Dosing interval**
Mild (60 - <90)	cefepime 2 g and enmetazobactam 0.5 g	Every 8 hours
Moderate (30- <60)	cefepime 1 g and enmetazobactam 0.25 g	Every 8 hours
Severe (15- <30)	cefepime 1 g and enmetazobactam 0.25 g	Every 12 hours
End stage renal disease (<15)	cefepime 1 g and enmetazobactam 0.25 g	Every 24 hours
Patients requiring hemodialysis	cefepime 1 g and enmetazobactam 0.25 g loading dose on the first day of therapy and cefepime 0.5g and enmetazobactam 0.125 g thereafter (every 24 hours but after the haemodialysis session on haemodialysis days).	Every 24 hours
Patients undergoing continuous ambulatory peritoneal dialysis (CAPD)	cefepime 2 g and enmetazobactam 0.5 g	Every 48 hours

Hepatic impairment

No dose adjustment is necessary in patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy in children below 18 years of age has not yet been established. No data are available.

Method of administration

EXBLIFEP is administered via intravenous infusion.

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

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions have been reported with cefepime and cefepime-enmetazobactam (see section 4.3 and 4.8).

Patients who have a history of hypersensitivity to other beta-lactam antibiotics may also be hypersensitive to cefepime-enmetazobactam. Before treatment initiation, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to beta-lactam antibiotics (see section 4.3).

Cefepime-enmetazobactan should be administered with caution to patients with a history of asthma or allergic diathesis.

The patient must be carefully monitored during the first administration. If an allergic reaction occurs, treatment must be discontinued immediately and adequate emergency measures must be initiated.

Renal impairment

Dose adjustments should be made in patients with renal impairment who have an absolute eGFR less than 60 mL/min (see section 4.2).

Reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures (including nonconvulsive status epilepticus), and/or renal failure have been reported with cefepime/enmetazobactam when the dose has not been reduced in patients with renal impairment. In some cases, neurotoxicity was reported in patients with renal impairment despite dose adjustments.

Renal function should be monitored carefully if medicinal products with nephrotoxic potential, such as aminoglycosides and potent diuretics, are administered concomitantly with cefepime-enmetazobactam.

Clostridioides difficile associated diarrhoea (CDAD)

CDAD has been reported with cefepime-enmetazobactam, and may range in severity from mild diarrhoea to fatal colitis. CDAD must be considered in patients who present with diarrhoea during or subsequent to the administration of cefepime-enmetazobactam. Discontinuation of therapy with cefepime-enmetazobactam and the use of supportive measures together with the administration of specific treatment for *C. difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Non-susceptible organisms

The use of cefepime-enmetazobactam may result in overgrowth of non-susceptible organisms, which may require interruption of treatment or other appropriate measures.

Elderly

No dose adjustment based on age is required. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.

Limitations of the clinical data

Hospital-acquired pneumonia, including ventilator-associated pneumonia

The use of cefepime-enmetazobactam to treat patients with hospital-acquired pneumonia, including ventilator-associated pneumonia, is based on experience with cefepime alone and pharmacokinetic-pharmacodynamic analyses for cefepime-enmetazobactam.

Limitations of the spectrum of antibacterial activity

Cefepime has little or no activity against the majority of Gram-positive organisms and anaerobes (see sections 4.2 and 5.1). Additional antibacterial agents should be used when these pathogens are known or suspected to be contributing to the infectious process.

The inhibitory spectrum of enmetazobactam includes class A extended spectrum β-lactamases (ESBLs). Enmetazobactam does not reliably inhibit the class A carbapenemase *Klebsiella pneumoniae* carbapenemase (KPC) and does not inhibit class B, class C or class D beta-lactamases. Cefepime is generally stable to hydrolysis by class C AmpC and class D OXA-48 enzymes (see section 5.1).

Interference with serological testing

A positive direct or indirect Coombs test without evidence of haemolysis may develop during treatment with cefepime-enmetazobactam as seen with cefepime.

Cephalosporin antibiotics may produce a false-positive reaction for glucose in the urine with copper reduction tests (Benedict's or Fehling's solution or with Clinitest tablets), but not with enzyme-based tests (glucose oxidase) for glycosuria. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical interaction studies have been performed with enmetazobactam.
However, based on *in vitro* studies and considering routes of elimination, the pharmacokinetic interaction potential for enmetazobactam is low.

Concomitant treatment with bacteriostatic antibiotics may interfere with the action of beta-lactam antibiotics. Cephalosporin antibiotics can potentiate the action of coumarin anticoagulants as seen with cefepime.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 (see section 5.3). Enmetazobactam should only be used during pregnancy when clearly indicated and only if the benefit for the mother outweighs the risk for the child.

Breast-feeding

Physico-chemical data suggest excretion of cefepime-enmetazobactam in human milk and cefepime-enmetazobactam has been shown to be excreted in milk from rat. A risk to the newborns/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.

Fertility

The effects of cefepime and enmetazobactam on fertility in humans have not been studied. No impairment of fertility has been seen in male and female rats treated with cefepime or enmetazobactam (see section 5.3).

4.7 Effects on ability to drive and use machines

EXBLIFEP has moderate influence on the ability to drive and use machines.

Possible adverse reactions such as altered state of consciousness, dizziness, confusion or hallucinations may alter the ability to drive and use machines (see sections 4.4, 4.8 and 4.9).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions that occurred in the Phase 3 study were alanine aminotransferase (ALT) increased (4.8%), aspartate aminotransferase (AST) increased (3.5%), diarrhoea (2.9%), and infusion site phlebitis (1.9%). A serious adverse reaction of *Clostridioides difficile* colititis occurred in 0.2% (1/516).

Tabulated list of adverse reactions

The following adverse reactions have been reported with cefepime alone during clinical studies or post marketing surveillance and/or identified during Phase 2 or/and Phase 3 studies with cefepime-enmetazobactam.

Adverse reactions are classified according to System Organ Class, frequency, preferred term using MedDRA terminology. 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) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2. Frequency of adverse reactions by system organ class

System organ class	Frequency	MedDRA preferred term (PT)
Infections and infestations	Uncommon	*Clostridioides difficile* associated diarrhoea (CDAD), oral candidiasis[a], vaginal infection

System organ class	Frequency	MedDRA preferred term (PT)
	Rare	Candida infection[a]
Blood and lymphatic system disorders	Very common	Coombs test positive[a]
	Common	Prothrombin time prolonged[a], partial thromboplastin time prolonged[a], anaemia[a], eosinophilia[a]
	Uncommon	Thrombocytopenia, leukopenia[a], neutropenia[a]
	Not known	Aplastic anaemia[b], haemolytic anaemia[b], agranulocytosis[a]
Immune system disorders	Rare	Anaphylactic reaction[a], angioedema[a], dermatitis allergic
	Not known	Anaphylactic shock[a]
Metabolism and nutrition disorders	Not known	Urine glucose false positive[a]
Psychiatric disorders	Not known	Confusional state[a], hallucination[a]
Nervous system disorders	Common	Headache
	Uncommon	Dizziness
	Rare	Convulsion[a], paraesthesia[a], dysgeusia
	Not known	Coma[a], stupor[a], encephalopathy[a], altered state of consciousness[a], myoclonus[a]
Vascular disorders	Common	Infusion site phlebitis
	Rare	Vasodilation[a]
	Not known	Haemorrhage[b],
Respiratory, thoracic and mediastinal disorders	Rare	Dyspnoea[a]
Gastrointestinal disorders	Common	Diarrhoea
	Uncommon	Pseudomembranous colitis, colitis, vomiting, nausea,
	Rare	Abdominal pain, constipation
Hepatobiliary disorders	Common	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased, Alkaline phosphatase increased
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Erythema, urticaria, pruritus
	Not known	Toxic epidermal necrolysis[b], Stevens-Johnson syndrome[b], erythema multiforme[b]

System organ class	Frequency	MedDRA preferred term (PT)
Renal and urinary disorders	Uncommon	Blood urea increased, blood creatinine increased
	Not known	Renal failure[a], toxic nephropathy[b]
Reproductive system and breast disorders	Rare	Vulvovaginal pruritus
General disorders and administration site condition	Common	Infusion site reaction, injection site pain, injection site inflammation
	Uncommon	Pyrexia[a], infusion site inflammation
	Rare	Chills[a]
Investigations	Common	Amylase increased, lipase increased, lactate dehydrogenase increased

[a]: Adverse reactions reported only with cefepime alone.
[b]**:** Adverse reactions that are generally accepted as being attributable to other compounds in the class (class effects).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures (see section 4.8).

Management

Accidental overdosing has occurred when large doses were given to patients with impaired renal function (see sections 4.2 and 4.4).

In case of severe overdose, especially in patients with compromised renal function, haemodialysis will aid in the removal of cefepime and enmetazobactam from the body; peritoneal dialysis is of no value (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, other beta-lactam antibacterials, fourth generation cephalosporins ATC code: J01DE51

Mechanism 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 the class A carbapenemase KPC and does not inhibit class B, class C or class D beta-lactamases.

Resistance

Bacterial resistance mechanisms that could potentially affect cefepime-enmetazobactam include mutant or acquired PBPs, decreased outer membrane permeability to either compound, active efflux of either compound, and β-lactamase enzymes refractory to inhibition by enmetazobactam and able to hydrolyse cefepime.

Antibacterial activity in combination with other agents

No antagonism was demonstrated in *in vitro* medicinal product combination studies with cefepime-enmetazobactam and azithromycin, aztreonam, clindamycin, daptomycin, doxycycline, gentamicin levofloxacin, linezolid, metronidazole, trimethoprim-sulfamethoxazole, or vancomycin.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for cefepime-enmetazobactam 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 cefepime has been shown to best correlate with the percentage of time of the dosing interval in which the free active substance concentration was above the cefepime-enmetazobactam MIC (% fT >MIC). For enmetazobactam, the pharmacokinetic/pharmacodynamic (PK-PD) index is the percentage of time of the dosing interval in which the free active substance concentration was above a threshold concentration (% fT $>C_T$).

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against the pathogens listed under each indication that were susceptible to cefepime-enmetazobactam *in vitro*.

Complicated urinary tract infections including pyelonephritis

Gram-negative micro-organisms:
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*

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 cefepime and cefepime-enmetazobactam in the absence of acquired mechanisms of resistance:

Gram-negative micro-organisms:
- *Klebsiella aerogenes*
- *Klebsiella oxytoca*

- *Serratia marcescens*
- *Citrobacter freundii*
- *Citrobacter koseri*
- *Providencia rettgeri*
- *Providencia stuartii*
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Enterobacter cloacae*

Gram-positive micro-organisms:
- *Staphylococcus aureus* (methicillin-susceptible only)

In vitro data indicate that the following species are not susceptible to cefepime-enmetazobactam:
- *Enteroccocus* spp.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with EXBLIFEP in one or more subsets of the paediatric population in the treatment of infections caused by gram-negative organisms (for the targeted indications 'Treatment of complicated urinary tract infections (cUTI), including acute pyelonephritis', 'Treatment of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP)' and 'Treatment of patients with bacteraemia that occurs in association with or is suspected to be associated with any of the above infections') (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After intravenous (IV) administration of 2 g cefepime and 0.5 g enmetazobactam over 2 hours to patients with cUTI q8h, peak plasma concentrations (C_{max}) assessed on Day 1 and Day 7 were 87 – 100 mcg/ml and 17 – 20 mcg/ml for cefepime and enmetazobactam respectively.
There was no significant difference in C_{max} and AUC between healthy volunteers and cUTI patients in the population PK analysis.

Distribution

Cefepime and enmetazobactam are well distributed in bodily fluids and tissues including bronchial mucosa. Based on the population PK analysis, the total volume of distribution was 16.9 L for cefepime and 20.6 L for enmetazobactam.

The serum protein binding of cefepime is approximately 20% and is independent of its concentration in serum. For enmetazobactam the serum protein binding is negligible.

An epithelial lining fluid (ELF) study in healthy volunteers showed that cefepime and enmetazobactam have similar lung penetration up to 73% and 62% at 8 hours post start of infusion, respectively, with a biodistribution coefficient fAUC (ELF/plasma) over the entire 8h dosing interval of 47% for cefepime and 46% for enmetazobactam.

Biotransformation

Cefepime is metabolised to a small extent. The primary metabolite is N-methylpyrrolidine (NMP) which accounts for approximately 7% of the administered dose.

Enmetazobactam undergoes minimal hepatic metabolism.

Elimination

Both cefepime and enmetazobactam are primarily excreted via kidneys as unchanged substance.

The mean elimination half-life of cefepime 2 g and enmetazobactam 500 mg when administered in combination in cUTI patients were 2.7 hours and 2.6 hours, respectively.

Urinary recovery of unchanged cefepime accounts for approximately 85% of the administered dose. For enmetazobactam, approximately 90% of the dose was excreted unchanged in the urine over a 24-hour period. Mean renal clearance for enmetazobactam was 5.4 L/h and mean total clearance was 8.1 L/h.

There is no accumulation of cefepime or enmetazobactam following multiple intravenous infusions administered every 8 hours for 7 days in subjects with normal renal function.

Linearity/non-linearity

The maximum plasma concentration (C_{max}) and area under the plasma active substance concentration time curve (AUC) of cefepime and enmetazobactam proportionally increased with dose across the dose range studied (1 gram to 2 grams for cefepime and 0.6 grams to 4 grams for enmetazobactam) when administered as a single intravenous infusion.

Special populations

Elderly

Cefepime pharmacokinetics have been investigated in elderly (65 years of age and older) men and women. Safety and efficacy in elderly patients was comparable to that in adults, while the elimination half-life was slightly longer and renal clearance lower in elderly patients. Dose adjustment is necessary in elderly patients with reduced renal function (see sections 4.2 and 4.4).

Population PK analysis for enmetazobactam did not demonstrate any clinically relevant change in PK parameters in elderly patients.

Renal impairment

For cefepime, without dose adjustment AUC_{0inf} is approximately 1.9-fold, 3-fold, and 5-fold higher for subjects with mild, moderate, and severe renal impairment, respectively compared with subjects with normal renal function and 12-fold higher for subjects with ESRD who underwent dialysis before cefepime-enmetazabactam administration compared with subjects with normal renal function.

For enmetazobactam, without dose adjustment AUC_{0inf} is approximately 1.8-fold, 3-fold, 5-fold higher for subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function and 11-fold higher for subjects with ESRD who underwent dialysis before cefepime-enmetazabactam administration compared with subjects with normal renal function.

To maintain similar systemic exposures to those with normal renal function, dose adjustment is required (see section 4.2).

The average elimination half-life in haemodialysis volunteers (n=6), after dosing was 23.8 hours and 16.5 hours for cefepime and enmetazobactam, respectively. With haemodialysis, the dose should be administered immediately following completion of dialysis (see section 4.2). Haemodialysis increased systemic clearance in subjects with ESRD when dialysis was performed after dosing (clearance 2.1 L/h and 3.0 L/h for cefepime and enmetazobactam, respectively) compared to values when dialysis was performed before dosing (clearance for cefepime and enmetazobactam 0.7 L/h and 0.8 L/h, respectively).

For cefepime the half life was 19 hours for continuous ambulatory peritoneal dialysis.

Augmented renal clearance

Simulations using the population PK model demonstrated that patients with supra-normal creatinine clearance (> 150 mL/min) had a 28% decrease of systemic exposure compared to patients with normal renal function (80-150 mL/min). In this population, based on pharmacokinetic/pharmacodynamic considerations, prolongation of duration of infusion to 4 hours is recommended to maintain appropriate systemic exposure (see section 4.2).

Hepatic impairment

With single-dose administration of 1 g, the kinetics of cefepime was unchanged in patients with hepatic impairement.

Enmetazobactam undergoes minimal hepatic metabolism and has a low potential for altered PK in the presence of hepatic impairment. Thus, no dose adjustment is required.

Paediatric population

The pharmacokinetics of cefepime-enmetazobactam has not yet been evaluated in patients from birth to 18 years old.

5.3 Preclinical safety data

Cefepime

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproductive toxicity or genotoxicity. No long term studies were performed in the animal to assess the carcinogenic potential.

Enmetazobactam

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

General toxicity

Dose dependent liver findings in terms of hepatocellular accumulation of glycogen accompanied by increases in liver weights in rats and by single cell cystic degeneration/necrosis and increased cholesterol and liver enzyme levels in dogs were observed following 28 days of once daily intravenous administration of enmetazobactam alone.

The liver effects induced by enmetazobactam did not change or exacerbate when given together with cefepime. Following up to 4 weeks (in rats) and 13 weeks (in dogs) of once daily intravenous administration of enmetazobactam and cefepime, corresponding adverse liver effects (at least partially reversible) were observed at 250/500 mg/kg/day in rats (AUC_{0-24} 195 mcg*h/mL) and at 200/400 mg/kg/day in dogs (AUC_{0-24} 639 mcg*h/mL). These doses result in an exposure margin of 0.86-fold in rats and 2.8-fold in dogs compared to the exposure at the maximum recommended human dose (AUC_{0-24} 226 mcg*h/mL). At the NOAELs of 125/250 mg/kg/day in rats and 50/100 mg/kg/day in dogs the margin to the exposure at the maximum recommended human dose was 0.57-fold and 0.71-fold, respectively.

Reproductive toxicity

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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or solutions except those mentioned in section 6.6.

There is a physical-chemical incompatibility with the following antibiotics: metronidazole, vancomycin, gentamicin, tobramycin sulphate and netilmicin sulphate. Should concomitant therapy be indicated, such agents must be administered separately.

6.3 Shelf life

2 years.

After reconstitution

The reconstituted vial should be further diluted immediately.

After dilution

Chemical and physical in-use stability has been demonstrated for 6 hours at 2 °C to 8 °C followed by 2 hours at 25 °C.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 mL vial (Type I clear glass) with stopper (bromobutyl rubber) and flip-off seal.

Pack size of 10 vials.

6.6 Special precautions for disposal and other handling

This medicinal product is for intravenous infusion and each vial is for single use only.

Aseptic technique must be followed in preparing the infusion solution.

Preparation of doses

Cefepime-enmetazobactam is compatible with sodium chloride 9 mg/ml (0.9%) solution for injection, 5% glucose injection solution and a combination of glucose injection solution and sodium chloride injection solution (containing 2.5% glucose and 0.45% sodium chloride).

EXBLIFEP is supplied as a dry powder in a single-dose vial that must be reconstituted and further diluted prior to intravenous infusion as outlined below.

To prepare the required dose for intravenous infusion, reconstitute the vial as determined from **Table 3** below:

1. Withdraw 10 mL from an infusion bag of 250 mL (compatible injection solution) and reconstitute the cefepime-enmetazobactam vial.
2. Mix gently to dissolve. The reconstituted cefepime-enmetazobactam solution will have an approximate cefepime concentration of 0.20 g/mL and an approximate enmetazobactam concentration of 0.05 g/mL. The final volume is approximately 10 mL.
   CAUTION: THE RECONSTITUTED SOLUTION IS NOT FOR DIRECT INJECTION.

The reconstituted solution must be diluted further, **immediately**, in an infusion bag of 250 mL (compatible injection solution) before intravenous infusion. To dilute the reconstituted solution, withdraw the full or partial reconstituted vial content and add it back into the infusion bag according to **Table 3** below.

3. The intravenous infusion of the diluted solution must be completed within 8 hours, if stored under refrigerated conditions (i.e., at 2° C to 8 °C; where it has been refrigerated for less than 6 hours, prior to being allowed to reach room temperature and then administered at room temperature over a period of 2 or 4 hours).

Table 3: Preparation of cefepime-enmetazobactam doses

Cefepime/enmetazobactam dose	Number of vials to reconstitute	Volume to withdraw from each reconstituted vial for further dilution	Final volume of infusion bag
2.5 g (2 g / 0.5 g)	1	Entire content (approximately 10 mL)	250 mL
1.25 g (1 g / 0.25 g)	1	5.0 mL (discard unused portion)	245 mL
0.625 g (0.5 g / 0.125 g)	1	2.5 mL (discard unused portion)	242.5 mL

Inspect the vial before use. It must only be used if the solution is free from particles. Use only clear solutions.

Like other cephalosporins, cefepime-enmetazobactam solutions can develop a yellow to amber color, depending on storage conditions. However, this has no negative influence on the effect of the product.

The prepared solution should be administered via intravenous infusion.

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

7. MARKETING AUTHORISATION HOLDER

Advanz Pharma Limited
Unit 17 Northwood House
Northwood Crescent
Dublin 9
D09 V504
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1794/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

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

Infosaúde - Instituto De Formação E Inovação Em Saúde S.A.
Rua Das Ferrarias Del Rei,
nº6 - Urbanização da Fábrica da Pólvora,
Barcarena,
2730-269,
Portugal

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

EXBLIFEP 2 g/0.5 g powder for concentrate for solution for infusion
cefepime/enmetazobactam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains cefepime dihydrochloride monohydrate equivalent to 2 g cefepime and 0.5 g of enmetazobactam.

3. LIST OF EXCIPIENTS

L-arginine.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For intravenous use after reconstitution and dilution.

For single use only

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Keep the vial in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Advanz Pharma Limited
Unit 17 Northwood House
Northwood Crescent
Dublin 9
D09 V504
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1794/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

EXBLIFEP 2 g/0.5 g powder for concentrate
cefepime/enmetazobactam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains cefepime dihydrochloride monohydrate equivalent to 2 g cefepime and 0.5 g of enmetazobactam.

3. LIST OF EXCIPIENTS

L-arginine.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For IV use after reconstitution and dilution.

For single use only

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Keep the vial in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Advanz Pharma Limited
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1794/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

EXBLIFEP 2 g/0.5 g powder for concentrate for solution for infusion
cefepime/enmetazobactam

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What EXBLIFEP is and what it is used for

EXBLIFEP is an antibiotic. It contains two active substances:
- cefepime, which belongs to a group of antibiotics called fourth generation cephalosporins and can kill certain bacteria;
- enmetazobactam, which blocks the action of enzymes called beta-lactamases. These enzymes make bacteria resistant to cefepime by breaking down the antibiotic before it can act. By blocking the action of beta-lactamases, enmetazobactam makes cefepime more effective at killing bacteria.

EXBLIFEP is used in adults to treat:
- complicated (severe) infections within the urinary tract (bladder and kidneys)
- certain types of pneumonia (infection of the lungs) that occur during a hospital stay

Exblifep is also used to treat bacteraemia (the presence of bacteria in the blood) due to, or possibly due to, any of the infections listed above.

2. What you need to know before you use EXBLIFEP

Do not use EXBLIFEP
- if you are allergic to cefepime, enmetazobactam or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to cephalosporins, which are antibiotics used to manage a wide range of infections.
- if you have had a severe allergic reaction (e.g., severe skin peeling; swelling of the face, hands, feet, lips, tongue or throat; or difficulty swallowing or breathing) to so-called beta-lactam antibiotics (antibiotics such as penicillins, carbapenems or monobactams).

Warnings and precautions

Talk to your doctor or pharmacist **before** using EXBLIFEP if:
- you are allergic to cephalosporins, penicillins or other antibiotics (see 'Do not use Exblifep')
- you have or have had asthma or are sensitive to have allergic reactions. Your doctor will check for any signs of allergies the first time you are given this medicine (see section 4).
- you have kidney problems. Your doctor may need to change the dose of this medicine.
- you have any upcoming blood or urine tests scheduled. This medicine can alter the results of some tests (see section 4).

Talk to your doctor or pharmacist **while** using EXBLIFEP if:
- you develop severe and persistent diarrhoea during or right after treatment. This may be a sign of an inflammation of the large bowel and needs urgent medical intervention.
- you suspect to have developed a new infection during prolonged use of EXBLIFEP. This may be caused by micro-organisms which are insensitive to cefepime and may require interruption of EXBLIFEP treatment.

Children and adolescents
This medicine should not be given to children under 18 years old because there is not enough information on its use in this age group.

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

In particular, tell your doctor if you use the following:
- other antibiotics, in particular aminoglycosides (such as gentamicin) or 'water tablets' (diuretics, such as furosemide). If you are using these medicines, your kidney function should be monitored.
- medicines that are used to prevent your blood from clotting (coumarin anticoagulants, such as warfarin). Their effect may be greater when you take Exblifep.
- certain types of antibiotics (bacteriostatic antibiotics). These can affect how well EXBLIFEP works.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Your doctor will advise if you should receive EXBLIFEP during pregnancy.

Exblifep may pass into breast milk. If you are breast-feeding, your doctor will advise you on whether you should stop breast-feeding or abstain from EXBLIFEP therapy, taking into account the benefit of breast-feeding for your child and the benefit of therapy for you.

Driving and using machines
This medicine may cause dizziness, which can affect your ability to drive and use machines. Do not drive or use machines until you no longer feel dizzy.

3. How to use EXBLIFEP

Your doctor or other healthcare professional will give you this medicine as an infusion (drip) into a vein (directly into the bloodstream). Depending on the type of infection that you have and your kidney function the infusion will be given during two or four hours.

The recommended dose is one vial (2 g of cefepime and 0.5 g enmetazobactam) every 8 hours.

Treatment normally lasts between 7 and 14 days, depending on the severity and location of the infection and on how your body responds to the treatment.

If you have kidney problems, your doctor may need to reduce the dose or change how often EXBLIFEP is given to you (see section 2: Warnings and precautions).

If you use more EXBLIFEP than you should
As this product is given by a doctor or other healthcare professional, it is unlikely that you will be given too much EXBLIFEP. However, let your doctor or nurse know immediately if you have any concerns.

If you forget to use EXBLIFEP
If you think you have not been given a dose of EXBLIFEP, tell your doctor or other healthcare professional immediately.

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

4. Possible side effects

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

Tell your doctor straight away if you experience the following side effects, as you may need urgent medical treatment:

Rare: may affect up to 1 in 1 000 people
- anaphylactic (allergic) reaction and angioedema. This may be life-threatening. Signs and symptoms may be a sudden swelling of your lips, face, throat or tongue; a severe rash; and, swallowing or breathing problems.

Not known: frequency cannot be estimated from the available data
- Stevens-Johnson syndrome and toxic epidermal necrolysis. Extremely intense and serious skin reactions. The adverse reaction of the skin may appear as rashes with or without blisters. Skin irritation, sores or swelling in the mouth, throat, eyes, nose and around the genitals and fever and flulike symptoms may occur. The skin rashes may develop into serious widespread skin damage (peeling of the epidermis and superficial mucous membranes) with life-threatening consequences.

Other side effects
Other side effects which may occur after Exblifeb treatment include those listed below

Very common : may affect more than 1 in 10 people
Side effect seen in blood tests:
- positive Coombs test (a blood test checking for antibodies that attack your body’s red blood cells)

Common: may affect up to 1 in 10 people
- infusion site phlebitis (inflammation at the site of infusion, causing pain, swelling and redness along a vein)
- reaction, pain and inflammation at the infusion site
- diarrhoea
- skin rash
- headache

Side effects seen in blood tests:
- increased liver enzyme levels in the blood
- increased levels of bilirubin (a substance produced by the liver) in the blood
- increased levels of amylase (an enzyme that helps the body digest carbohydrates) in the blood
- increased levels of lipase (an enzyme that helps the body digest fat) in the blood

- increased levels of lactate dehydrogenase (a marker indicating cell and tissue damage in the body) in the blood
- changes in your white blood cell count (*eosinophilia*)
- low levels of red blood cells (*anaemia*)
- blood coagulation delayed (increased time for blood to clot)

Uncommon: may affect up to 1 in 100 people
- *clostridioides difficile*-associated diarrhoea (CDAD), painful, severe diarrhoea caused by a bacteria called clostridioides difficile
- fungal infection in the mouth
- vaginal infection
- inflammation of the large intestine, causing diarrhoea, usually with blood and mucus
- dizziness, nausea, vomiting
- reddening of the skin, hives, iching
- fever
- infusion site inflammation

Side effects seen in blood tests:
- low levels of certain blood cells (*leucopenia, neutropenia, thrombocytopenia*)
- increased levels of urea and creatinine (measures indicating reduced kidney function) in the blood

Rare: may affect up to 1 in 1 000 people
- shortness of breath
- stomach pain, constipation
- fungal infection
- convulsion (fits)
- distortion of the sense of taste
- sensation of pricking or numbness of your skin, pins and needles
- itching in and around the vaginal area
- allergic dermatitis
- chills
- widening of blood vessels in the body

Not known: frequency cannot be estimated from the available data
- coma
- reduced consciousness
- encephalopathy (a brain disorder caused by harmful substance or infection)
- altered state of consciousness
- muscle jerks
- confusion, hallucinations
- false positive urinary glucose tests
- kidney problems (failure or any other structural changes or dysfunction)
- bleeding
- erythema multiforme (a skin rash, which may blister, and looks like small targets (central dark spot surrounded by a paler area, with a dark ring around the edge).

Side effects seen in blood tests:
- very low levels of granulocytes, a type of white blood cells (*agranulocytosis*)
- red blood cells destroyed too quickly (*haemolytic anaemia*)
- low levels of red blood cells caused by the inability of your bone marrow to make enough new cells *(aplastic anaemia)*

Reporting of side effects

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

5. How to store EXBLIFEP

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

Do not use this medicine after the expiry date which is stated on the carton and vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials: Store in a refrigerator (2 ºC – 8 ºC). Keep the vial in the outer carton in order to protect from light.

After reconstitution and dilution: Store in a refrigerator (2 ºC – 8 ºC) for not more than 6 hours before use.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What EXBLIFEP contains
- The active substances are cefepime and enmetazobactam.
- Each vial contains cefepime dihydrochloride monohydrate equivalent to 2 g cefepime and 0.5 g enmetazobactam.
- The other ingredient is L-arginine.

What EXBLIFEP looks like and contents of the pack
EXBLIFEP is a white to yellowish powder for concentrate for solution for infusion (powder for concentrate) supplied in a 20 mL glass vial with a bromobutyl rubber stopper and flip-off seal.

Pack size of 10 vials.

Marketing Authorisation Holder
Advanz Pharma Limited
Unit 17 Northwood House
Northwood Crescent
Dublin 9
D09 V504
Ireland
+44 (0)208 588 9131
medicalinformation@advanzpharma.com

Manufacturer
Infosaúde - Instituto De Formação E Inovação Em Saúde S.A.
Rua Das Ferrarias Del Rei,
nº6 - Urbanização da Fábrica da Pólvora,
Barcarena,
2730-269,
Portugal

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Preparation of solution

This medicinal product is for intravenous infusion and each vial is for single use only.

Aseptic technique must be followed in preparing the infusion solution.

Preparation of doses

Cefepime-enmetazobactam is compatible with sodium chloride 9 mg/ml (0.9%) solution for injection, 5% glucose injection solution and a combination of glucose injection solution and sodium chloride injection solution (containing 2.5% glucose and 0.45% sodium chloride).

EXBLIFEP is supplied as a dry powder in a single-dose vial that must be reconstituted and further diluted prior to intravenous infusion as outlined below.

To prepare the required dose for intravenous infusion, reconstitute the vial as determined from **Table 1** below:

1. Withdraw 10 mL from an infusion bag of 250 mL (compatible injection solution) and reconstitute the cefepime-enmetazobactam vial.
2. Mix gently to dissolve. The reconstituted cefepime-enmetazobactam solution will have an approximate cefepime concentration of 0.20 g/mL and an approximate enmetazobactam concentration of 0.05 g/mL. The final volume is approximately 10 mL.
   CAUTION: THE RECONSTITUTED SOLUTION IS NOT FOR DIRECT INJECTION.

The reconstituted solution must be diluted further, **immediately**, in an infusion bag of 250 mL (compatible injection solution) before intravenous infusion. To dilute the reconstituted solution, withdraw the full or partial reconstituted vial content and add it back into the infusion bag according to **Table 1** below.

3. The intravenous infusion of the diluted solution must be completed within 8 hours, if stored under refrigerated conditions (i.e., at 2 °C to 8 °C; where it has been refrigerated for less than 6 hours, prior to being allowed to reach room temperature and then administered at room temperature over a period of 2 or 4 hours).

Table 1: Preparation of cefepime-enmetazobactam doses

Cefepime/enmetazobactam dose	Number of vials to reconstitute	Volume to withdraw from each reconstituted vial for further dilution	Final volume of infusion bag
2.5 g (2 g / 0.5 g)	1	Entire content (approximately 10 mL)	250 mL
1.25 g (1 g / 0.25 g)	1	5.0 mL (discard unused portion)	245 mL
0.625 g (0.5 g / 0.125 g)	1	2.5 mL (discard unused portion)	242.5 mL

Inspect the vial before use. It must only be used if the solution is free from particles. Use only clear solutions.

Like other cephalosporins, cefepime-enmetazobactam solutions can develop a yellow to amber colour, depending on storage conditions. However, this has no negative influence on the effect of the product.

The prepared solution should be administered via intravenous infusion.

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