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Cefepime-Enmetazobactam: A Novel B-Lactam/B-Lactamase Inhibitor Combination for Complicated Urinary Tract Infections

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ABSTRACT
The growing problem of infections due pathogens with antimicrobial resistance,infections (UTIs) and other serious infections.1,2 However, an increasing prevalence of extended-spectrum β-lactamases, which cause resistance to most β-lactams except carbapenems, limits the therapeutic benefit of β-lactams.3,4 Prescribing piperacillin/tazobactam for infections that may be caused by extended-spectrum β-lactamase–producing bacteria may not be appropriate. New therapeutic options, especially Gram-negative bacteria, have led to the development of new β-lactam/β-lactamase inhibitor combination antibiotics. During the last 2 years from the writing of this article, cefepime/ enmetazobactam, aztreonam/avibactam, and sulbactam/durlobactam were approved for use in clinical practice. Cefepime/enmetazobactam targets extended-spectrum β-lactamase (ESBL)-producing Pseudomonas aeruginosa and Enterobacterales. It is indicated for the treatment of patients with complicated urinary tract infections, including pyelonephritis, in Europe and the USA, and also for hospital-acquired pneumonia, ventilator-associated pneumonia, and bacteremia associated with those infections (only in Europe). The antimicrobial spectrum of aztreonam/avibactam includes carbapenem-resistant Enterobacterales. Aztreonam/avibactam is indicated for the treatment of adult patients who suffer from complicated intra-abdominal infections, complicated urinary tract infections including pyelonephritis, hospital-acquired pneumonia, and ventilator-associated pneumonia due to aerobic Gram-negative infections with limited therapeutic options. Sulbactam/ durlobactam, a combination of 2 β-lactamase inhibitors, is indicated for the treatment of adult patients with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia due to the Acinetobacter baumannii–calcoaceticus complex [including carbapenem-resistant Acinetobacter baumannii (CRAB) infections]1
As a library, NLM provides access to scientific literature. Inclusion in an NLM database does not involve severe infections. The increased rate of resistance towards different classes limits their treatment options. The aim of this study was to assess the in vitro activity of classical and novel combinations of β-lactam/β-lactamase inhibitors against E. coli clinical isolates.
140 clinical isolates of E. coli were collected from clinical specimens from Gastrointestinal Surgery Center (GISC) in Egypt. Extended spectrum β-lactamase (ESBL) was detected by double disk synergy test. Furthermore, the minimum inhibitory concentrations (MICs) for five different combinations were determined using the broth microdilution method including: amoxicillin/clavulanate and ampicillin/sulbactam as an example for classical combinations and cefoperazone/sulbactam, ceftazidime/avibactam, and cefepime/ enmetazobactam as an example for new combinations.
The percentage of ESBL production among the tested isolates was 46.4%. Isolates were highly resistant to classical β-lactam/β-lactamase inhibitor combinations, where (40.7%) and (42.9%) of isolates were resistant to amoxicillin/clavulanate and ampicillin/sulbactam, respectively. While new β-lactam/β-lactamase inhibitor combinations had promising inhibitory action. The addition of novel β-lactamase inhibitors restored the susceptibility of isolates, where (94.3%) of isolates became susceptible to ceftazidime/avibactam combination, followed by cefoperazon

Keywords: Complicated urinary tract infections, Cefepime-Enmetazobactam, ESBL-producing pathogens, β-lactamase inhibitor, Antimicrobial resistance, Carbapenem-sparing therapy

I. INTRODUCTION

Cefepim enmetazobactam a novel intravenous B lactam inhibitors combination was approved by the food and drug administration February 2024 for the treatment complicated urinary tract infections(1)

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Cefepime is a 4th-generation cephalosporin that has broad spectrum bactericidal activity against gram negative and gram positive pathogen(2)

Enmetazobactam in compound in a penicillin acid sulphon b lactamase inhibitors in a structure same tazobactam methyl group in zwitterion ion form Good activity in present in tetrazol ring [3]

Klebsiella pneumoniae is among the leading causes of healthcare-associated infections in hospitals globally and is primarily of concern in hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) in critically ill patients [4]

Extended-spectrum β-lactamases (ESBLs) are a diversified group of enzymes that confer resistance to third- and fourth-generation cephalosporins The prevalence of ESBL-producing Enterobacteriaceae has risen globally , prompting the World Health Organization to list these pathogens as a priority for devel

Extended-spectrum β-lactamases (ESBLs) are a diversified group of enzymes that confer resistance to third- and fourth-generation cephalosporins (5).The prevalence of ESBL-producing Enterobacteriaceae has risen globally (2–5), prompting the World Health Organization to list these pathogens as a priority for development of new therapies (opment of new therapies [5] [6].

Although piperacillin-tazobactam has been a β-lactam/β-lactamase inhibitor (BL/BLI) mainstay for treating serious infections[6]

β-lactam antibiotics are among the most commonly prescribed antimicrobials worldwide, making up 65% of the global antibiotics market with annual sales of approximately $15 billion [7].

β-lactam antibiotics are the largest class of antibiotics; this class is further subdivided into penicillins, cephalosporins, carbapenems, and monobactams. They bind to and inactivate the transpeptidase domain of penicillin-binding proteins (PBPs) and thus inhibit bacterial cell wall synthesis [**8].**

Se EXBLIFEP received FDA approval to treat adults (18 years and older).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefepim injection and other antibacterial drug[10].

Cefepim-Enmetazobactam overview

Cefepim DRUG

Cefepime, a fourth-generation cephalosporin antibiotic, is distinguished by its broad-spectrum activity primarily against Gram-negative bacteria, including certain strains producing extended-spectrum β-lactamases (ESBLs).13 Its bactericidal mechanism of action involves penetration of bacterial cell walls and selective binding to penicillin-binding proteins (PBPs), particularly PBP3, thereby disrupting peptidoglycan synthesis and inducing bacterial cell lysis.(11)

CHEMICAL COMPOSITION

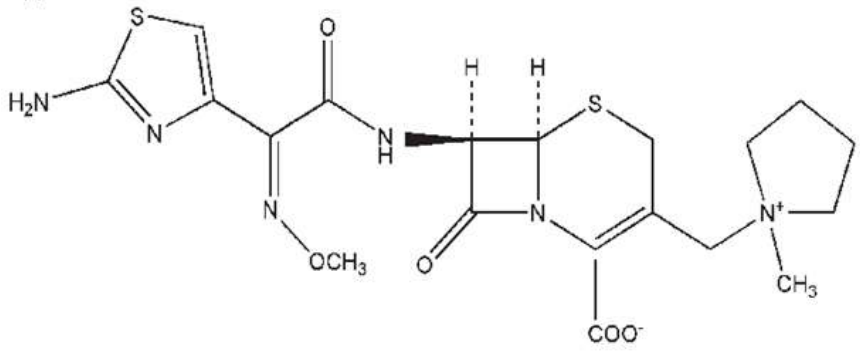

Figure (1)

Cefepime, present as cefepime hydrochloride monohydrate, is a white to pale yellow powder. The chemical name for cefepime is (6R,7R, Z) -7-(2-(2-aminothiazol-4-yl)-2-(methoxyimino) acetamido)-3-((1-methylpyrrolidinium-1-yl) methyl)-8-oxo-5-thia-1-aza-bicyclo (4.2.0) oct-2-ene-2-carboxylate. Its chemical structure is shown in Figure (12).

Enmetazobactam DRUG

Enmetazobactam is a novel beta-lactamase inhibitor used in combination with cefepime (a cephalosporin antibiotic) to treat bacterial infections, specifically those caused by multi-drug

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resistant Gram-negative bacteria. It is part of the fixed-dose combination medication,

CHEMICAL COMPOSITION

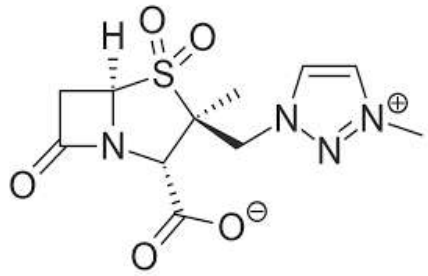

Figure (2)

Enmetazobactam is a white to off-white powder, with a molecular weight of 314.38. The chemical name for Enmetazobactam is (2S,3S,5R)-3-methyl-3-((3-methyl-1H-1,2,3-triazol-3-ium-1-yl) methyl)-7-oxo-4-thia-1-azabicyclo (3.2.0) heptane-2-carboxylate 4,4-dioxide, its chemical structure is shown in Figure 2 (13)

1.COMBINATION THERAPY

Cefepime/enmetazobactam, marketed as Exblifep, is a fixed-dose combination antibiotic used to treat infections caused by multidrug-resistant Gram-negative bacteria.

table 1

Generic name	Brand name	DRUG approval	Antibiotics class	Antimicrobial spectrum	Site of infections
Cefepim Enmetazobactam	EXBLIFEP	FDA, EMA	Fourth generation of cephalosporin Penicillin acid sulphon	ESBL producing pseudomonas aeruginosa and Enterobacterales Escherichia coli klebsiella pneumonia proteus mirabilis and enterobacter cloacae	cUTI including pyelonephritis FDA, EMA HAP, VAP bacteremia associated with those infections EMA
Aztreonam/ Avibactam	EMBLAVEO	EMA	Monocyclic B-lactam broad spectrum B-lactamase inhibitors	Enterobacterales including those that produce ESBLs serine metallo B-lactamase inhibitors	cIAI cUTI including pyelonephritis HAP VAP aerobic gram negative infections
Salbactam/ durlobactam	XACDRO	FDA	B-lactamase inhibitors	acinetobacter baumannii calcoaceticus complex	HABP and VABP in patients older than 18 years

Cefepim/ enmetazobactam DRUG ina route administration of intravenous iv route (14).

EXBLIFEP FDA APPROVAL History

Exblifep (cefepime and enmetazobactam) is a fourth generation cephalosporin and beta lactamase inhibitor combination for the treatment of complicated urinary tract infections (cUTIs).

Exblifep is indicated for the treatment of patients 18 years and older with complicated urinary tract infections (cUTI) including pyelonephritis caused by designated susceptible microorganisms.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Exblifep and other antibacterial drugs, Exblifep should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

1. A simple UTI (or simple cystitis) is an infection of the urinary tract typically seen in afebrile, non-pregnant, immune-competent female patients. A complicated UTI is any UTI other than a simple UTI and includes UTIs in immunocompromised patients, males, pregnant patients, and those associated with fevers, stones, sepsis, urinary obstruction, catheters, or involving the kidneys.
2. Exblifep is designed to combat anti-microbial resistance in gram-negative bacteria, especially resistance mediated by Extended Spectrum Beta Lactamases (or ESBLs).

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3. FDA approval of Exblifep was supported by clinical data that demonstrated Exblifep's effectiveness against antimicrobial resistance in gram-negative bacteria, especially resistance mediated by both ESBL (Extended Spectrum Beta Lactamases) and AmpC. This included results from Allecra's Phase 3 ALLIUM trial, which met criteria for non-inferiority and superiority compared to piperacillin/tazobactam in the primary composite outcome of clinical cure and microbiological eradication in patients with cUTIs.
4. Exblifep is administered by intravenous infusion over 2 hours, every 8 hours for 7 days to 14 days.
5. Warnings and precautions associated with Exblifep include hypersensitivity reactions, neurotoxicity, and clostridioides difficile-associated diarrhea.
6. Common adverse reactions include increased transaminases, increased bilirubin, headache, and phlebitis/infusion site reaction
7. Common adverse reactions include increased transaminases, increased bilirubin, headache, and phlebitis/infusion site reactions (15).

2.MEDICINAL ACTIVITY

Cefepim DRUG CHEMISTRY

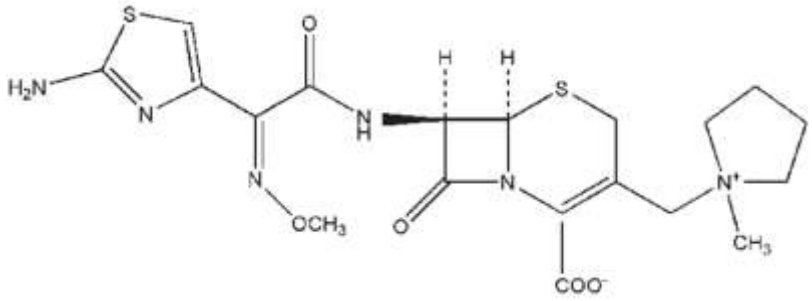

Figure (3)

Cefepime contains the β-lactam ring fused with a dihydrothiazine ring, forming the typical cephem nucleus, characteristic of cephalosporin antibiotics.

3.Zwitterionic Nature: carboxy group on the dihydrothiazine ring (acidic) .quaternary ammonium group +N(CH3)-pyrolidine on the side chain (basic)

Function group and substituents

1. B-lactam ring (azetidin-2-one)

Four-membered ring critical for antibacterial activity.

Responsible for inhibiting bacterial cell wall synthesis.

2.dihydrothiazine ring: six members sulfur containing ring fused to the B-lactam

4.oxime group: (-CH=NOCH3): located -7-position acyl side chain provide resistance the B-lactamase.the methoxyimino group (OCH3) is key for B-lactamase stability

5.aminothiazole ring: the 2-amino-4-thiazoyl group on the acyl side chain increase activity against gram negative bacteria and improve affinity to penicillin-binding protein PBs (16)

ENMETAZOBACTAM DRUG CHEMISTRY

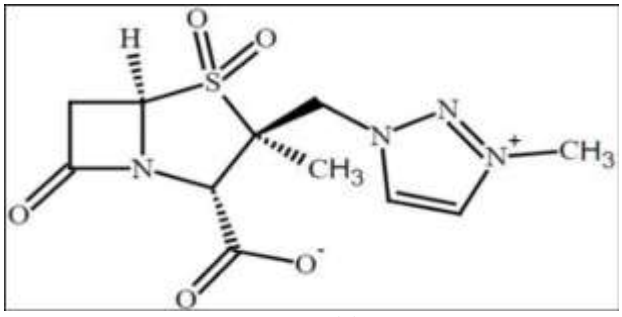

Figure (4)

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Penicillianic acid sulphon derivatives.a bicyclic compound with a triazolidium ring and [3.2.0] bicyclic core.
N- methylated, making it structurally similar to tazobactam.(17)

3. Pharmacology
MECHANISMS ACTION
Cefepim bind to and inhibit PBP2 and PBP3 (18)
Enmetazobactam irreversibly bind to and inactivates ambler class A-B lactamase.(19)

Cefepim enmetazobactam combination that was shown to be as effective as carbapenams against ESBL in vitro, in addition that combination in active against class A,C and D and B-lactamase while it does not enhance the potency of cefepim against p.aeruginosa. (20).

Inhibit B-lactamase enzyme preventing bacteria resistance

Restore cefepim activity against resistance bacteria like Escherichia coli, klebsiella, pneumonia and pseudomonas aeruginosa targeted extended spectrum B-lactamase ESBL making it effective against ESBL producing Enterobacterales.

It is important to note that enmetazobactam exhibits limited capacity to inhibit Ambler Class C or Class D β-lactamases, although there are instances where it can exert a degree of inhibitory effect on the OXA-1 enzyme variant. The remarkable stability of cefepime in the presence of Class C and D β-lactamases is a significant factor, as it allows for the synergistic combination of cefepime and enmetazobactam to maintain efficacy against a wide range of β-lactamases classified as Class A, C, and D. Consequently, this combined therapeutic approach not only enhances the antimicrobial effectiveness but also provides a strategic advantage in combating bacterial resistance mechanisms that are increasingly prevalent in clinical settings. Therefore, the interplay between these two pharmacological agents exemplifies a promising avenue for the development of effective treatment regimens against multidrug-resistant bacterial pathogens.(21).

Inhibition resistance SBLs since the clinical introduction of the pioneering SBLi B lactamase have evolved and SBLi use is increasingly compromised by extended spectrum B-lactamase ESBLs and inhibition resistance SBLs.

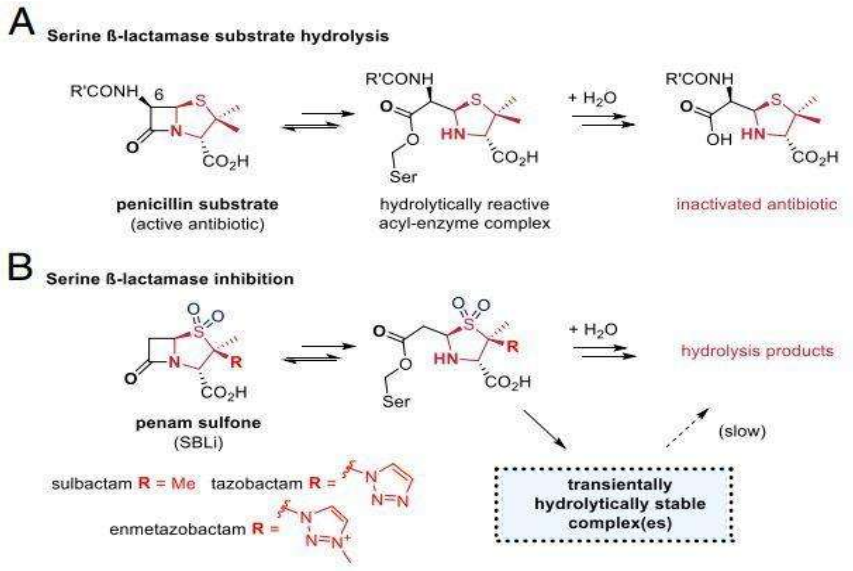

Fig. 1. Sulfone derivatives of penicillins are potent clinically used mechanism-based inhibitors of SBLs. (*A*) Outline mechanism for penicillin hydrolysis as catalyzed by SBLs; reaction proceeds via an AEC, which is efficiently hydrolyzed. (*B*) Sulfone derivatives of penicillins are SBLi that react to give one or more hydrolytically stable complex(es), the nature of which was the focus of our work.

Figure 5 (22)

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MECHANISMS OF RESISTANCE

Cefepim/enmetazobactam typically exhibit susceptibility to hydrolytic degradation and inactivation by carbapenams.

Although there exists a degree of stability against hydrolysis facilitated by kpc and oxA-48 like enzymes.

The penetration of cefepim into bacterial cells is contingent upon the porin channel notably outer membrane proteins F (ompf) is Escherichia coli.(23).

PHARMACOKINETICS

Pharmacokinetic (PK) Parameters

The pharmacokinetic properties of cefepime and enmetazobactam are summarized in Table 5 as mean (SD) in patients with cUTI and eGFR greater than or equal to 60 mL/min.

Table 5: Pharmacokinetic Parameters (Mean [SD]) of Cefepime and Enmetazobactam(24).

Absorption

Rapidly absorbed after intramuscular injection with peak concentration typically reached within 6 hours

Distribution

The average steady state volume of distribution is about 18 L.

Elimination

Primarily excreted unchanged in the urine 85%

Half life

2 hours

Enmetazobactam

Absorption

Not applicable as it administration intravenous

Elimination

Primarily excreted unchanged in the urine (about 90%)

Half life around 2.6 hours (25)

Table 2 (26)

PHARMACOKINETICS PARAMETERS	CEFEPIM	ENMETAZOBACTAM
Exposure		
Cmax (µg/mL)1	99.8(26.4)	19.8(6.3)
AUClast (µg•h/mL)1	379.5(123.3)	75.3(30.8)
DISTRIBUTION		
% Bound to human plasma proteins	20%	Negligible
Vss(L)	20.02	25.26
PROPORTIONALITY	Exposure approximately proportional to dose following IV administration	Exposure approximately proportional to dose following IV administration
ACCUMULATION	Similar pharmacokinetics following single and multiple dosing	Similar pharmacokinetics following single and multiple dosing
ELIMINATION		
CL(L/h)	5.8(1.9)	7.8(2.6)
T1/2(h)	2.7(1.1)	2.6(1 1)
METABOLISM	Minimally metabolized	Minimally metabolized
EXCRETION Major route of administration	Renal	Renal
%excreated unchanged in urine	85%	90%

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PHARMACODYNAMIC

Similar to other beta-lactam antibacterial drugs, the percentage of time that unbound plasma concentrations of cefepime exceed the cefepime-enmetazobactam minimum inhibitory concentration (MIC) against the infecting The organism has been shown to best correlate with efficacy in animal and in vitro models of infection. The percentage of time that enmetazobactam concentrations exceed a threshold concentration is the index that best predicts efficacy of enmetazobactam in combination with cefepime in animal and in vitro models of infection.

Cardiac Electrophysiology

At approximately 12 times the peak enmetazobactam concentrations of the maximum recommended dosing regimen of EXBLIFEP, clinically significant QTc interval prolongation was not observed.(27)

Cefepim

Cefepime is a fourth-generation cephalosporin antibiotic.5,6 It is active against Gram-negative bacteria such as Enterobacter spp., Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis and Pseudomonas aeruginosa, and Gram-positive bacteria such as Staphylococcus aureus (methicillin-susceptible isolates only), Streptococcus pneumoniae, Streptococcus pyogenes and Viridans group streptococci.5,6 Compared to third-generation cephalosporins, cefepime has an extended Gram-negative coverage. Whereas other cephalosporins are degraded by plasmid- and chromosome-mediated beta-lactamases, cefepime is stable and not significantly hydrolyzed by these enzymes.1,4 Cefepime is also a poor inducer of type 1 beta-lactamases and, therefore, a good alternative against bacteria resistant to third-generation cephalosporins.(26)

In animal models of infection, the time that the unbound plasma concentration of cefepime exceeds the minimum inhibitory concentration (MIC) of infecting organisms has been shown to correlate with treatment efficacy.5,6 It has been suggested that cefepime can cross the inflamed blood-brain barrier.5,6 This, along with its ability to inhibit γ-aminobutyric acid (GABA), could lead to the neurotoxic effects observed in some of the patients treated with cefepime.(28)

ENMETAZOBACTAM

Enmetazobactam is an antibacterial agent that is active against most gram-positive and gram-negative bacteria.

4.Clinical studies

Two phase studies and one phase -2 study have been completed (25)but have not yet been reported.(29)

A phase -3 multi- centre randomizer control trial compared cefepim/enmetazobactam to piperacillin / tazobactam for the treatment of complex urinary tract infections cUTI.

Participants were adults with i) pyuria, ii) at least two symptoms/signs of cUTI, with either at least one risk factor for developing cUTI or microbiologically confirmed infection, and iii) requiring hospitalization requiring at least 7 days of intravenous antibiotics.

The primary endpoint was a composite measure requiring resolution of baseline signs and symptoms (clinical cure) and reduction of baseline pathogen urinary concentration, if isolated, to <103 CFU/mL (microbiological cure) at day 14. Secondary outcomes included the composite outcome at day 3, end of treatment and day 21, clinical and microbiological cure assessed independently at day 3, end of treatment and days 14 and 21, and the primary composite outcome assessed in a range of pre-specified sub-groups, including those infected with an ESBL-producing pathogen. Microbiological recurrence was assessed as an exploratory outcome.

Cefepime/enmetazobactam was superior to piperacillin/tazobactam in the primary outcome (79.1% vs 58.9% composite cure rates). There was no significant difference between clinical cure rates alone, but the cefepime/enmetazobactam group achieved significantly greater microbiological eradication rates for all pathogens (82.9% vs 64.9%), and greater achievement of the composite measure where ESBL-producing Enterobacterales were the causative organism (73.7% vs 51.5%). There were no differences in adverse events. Microbiological recurrence was lower in patients receiving cefepime/enmetazobactam compared to those receiving piperacillin/tazobactam (11.35% vs 29.4%).

Serious adverse reactions and adverse reactions leading to discontinuation treatment was discontinued due to adverse reactions in 3% (13/516) of patients receiving EXBLIFEP and in 2% of patients receiving piperacillin/ tazobactam the most common adverse reactions leading to discontinuation EXBLIFEP were hypersensitivity nausea and increase transaminases each 0.4% the other adverse reactions resulting in discontinuation of EXBLIFEP were abdominal pain , bacteria infections,chest pain , eructation,fungal infections gastroenteritis, headache insomnia pneumonia

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restlessness and urinary retention each 0.2% death was reported in 0.6% patient who received piperacillin/ tazobactam.2/(30)

Table 3 select adverse reactions occurring in 1% or greater of UTI patient receiving EXBLIFEP in trial -1 (30).

Adverse reactions	EXBLIFEP N=516 N%	Piperacillin/tazobactam N=518 N%
Transaminases increased	101(20)	103(20)
Bilirubin increased	36(7)	21(4)
Headache	26(5)	12(2)
Phlebitis infusion site reactions	24(5)	12(2)
Diarrhoea	21(4)	26(5)
Anemia	16(3)	16(3)
Hypersensitivity	10(2)	3<1
Vomiting 9(2)	9(2)	6(1)
Nausea	6(1)	3(<1)

a. Transaminases increased includes alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, hepatic enzymes increased, liver function test increased, transaminases increased, and hypertransaminasemia.
b. Bilirubin increased include blood bilirubin increased, bilirubin conjugated increased, and hyperbilirubinemia.
c. Headache includes headache and tension headache.
d. Phlebitis/Infusion site reactions includes phlebitis, thrombophlebitis, thrombophlebitis superficial, injection site inflammation, Infusion site extravasation, injection site thrombosis, vessel puncture site pain, vessel puncture site hematoma, and rash erythematous
e. Anemia includes anemia, hypochromic anemia, iron deficiency anemia, and normocytic anemia.
f. Hypersensitivity includes allergic cough, dermatitis allergic, hypersensitivity, periorbital edema, pruritus, rash, and urticaria.

The Trial was not designed to evaluate meaningful comparisons of the incidence of adverse reactions in the EXBLIFEP and piperacillin/tazobactam treatment group.

DOSE ADMINISTRATION

The recommended dosage of EXBLIFEP is 2.5 grams (2 grams cefepime and 0.5 grams enmetazobactam) administered every 8 hours by intravenous (IV) infusion over 2 hours in patients 18 years of age and older with an estimated glomerular filtration rate (eGFR) between 60 and 129 mL/min. The duration of treatment is 7 days and up to 14 days for patients with concurrent bacteremia.

Recommended dosage in patients (18-years of age and older) based on renal function

The recommended dosage of EXBLIFEP in patients 18 years of age and older with varying degrees of renal function is described in Table 1. For patients with changing renal function, monitor serum creatinine concentrations and eGFR at least daily and adjust the dosage of EXBLIFEP accordingly.(30)

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Table 4 recommended dosage forms of EXBLIFEP in patients (18 years of age and older) based on renal function)

eGFR ML/min	Recommended dosage regimen for EXBLIFEP cefepim enmetazobactam)	Dosing interval	Infusion time
Greater than or equal to 130	EXBLIFEP 2.5 gram (2 gram cefepim and 0.5 gram enmetazobactam)	every 8 hours	4 hours
90 to 129	EXBLIFEP 2.5 gram (2 gram cefepim and 0.5 gram enmetazobactam)	every 8 hours	2 hours
60 to 89	EXBLIFEP 2.5 gram (2 gram cefepim and 0.5 gram enmetazobactam)	every 8 hours	2 hours
30 to 59	EXBLIFEP 2.5 gram (2 gram cefepim and 0.5 gram enmetazobactam)	every 8 hours	2 hours
15 to 29	EXBLIFEP 2.5 gram (2 gram cefepim and 0.5 gram enmetazobactam)	12 hours	2 hours

A.preparation of EXBLIFEP for intravenous infusion administration

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. EXBLIFEP does not contain preservatives. Aseptic technique must be used for reconstitution and dilution. Prepare the required dose for intravenous infusion using the steps described below:

1.Reconstitute the powder in the EXBLIFEP vial, with 10 mL of 0.9% Sodium Chloride Injection, or 5% Dextrose Injection, or 2.5% Dextrose and 0.45% Sodium Chloride Injection, from a 250 mL infusion bag.

2.Mix gently to dissolve. The reconstituted EXBLIFEP solution will have a resultant concentration of 0.2 grams/mL (cefepime 0.16 grams/mL and enmetazobactam 0.04 grams/mL). The final volume is approximately 13 mL. The reconstituted solution is not for direct injection.

3.The reconstituted solution must immediately be diluted further in the 250 mL infusion bag used in Step 1. The same injection solution should be used for both reconstitution and dilution (e.g., if reconstitution in Step 1 is performed with 5% dextrose, the dilution in Step 3 should be performed with a 250 mL infusion bag of 5% dextrose). To dilute the reconstituted solution, withdraw the full or partial reconstituted vial contents and add it back into the infusion bag in accordance with Table 2 below.(31)

Table 5 preparation of EXBLIFEP dose

EXBLIFEP cefepim enmetazobactam dose	Number of vials to reconstituted for further dilution	Volume to withdraw from each reconstituted vial for further dilution	Volume of infusion bag
2.5 grams (2 grams cefepim and 0.5 grams enmetazobactam)	1 vial	entire content approximately 13 ml	250 mL
1.25 grams (1 grams cefepim enmetazobactam)	1 vial	Partial content (6.5 ml)	250 ml
0.625 grams (0.5 grams cefepim and 0.125 grams enmetazobactam)	1 vial	Partial content (3.3ml)	250 ml

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4.Store the prepared diluted solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 4 hours prior to administration. The intravenous infusion administration of the diluted solution must be completed within 6 hours of dilution.
5.Visually inspect the diluted EXBLIFEP solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The color of the EXBLIFEP infusion solution for administration is clear to yellowish. Discard unused portion after use (32)

Serious side effects
1.Abdominal pain
2.Bacterial infections
3.hypersensitivity reactions
4.chest pain
5.eructation
6.fungal infections
7.gastroenteritis
8.insomnia
9.pneumonia
10. restlessness
11.urinary retention (33)

Warning of precautions
Allergic reaction: Do not take it if you're allergic to cephalosporins, penicillins, or similar antibiotics.
Kidney problems: This drug can build up in people with kidney issues, so doctors adjust the dose as needed.
Brain effect: Can sometimes cause confusion, dizziness, or seizures, especially in elderly patients or those with kidney problems.
Severe diarrhoea: May cause an overgrowth of bad bacteria in the gut (Clostridioides difficile).
Drug interactions; Avoid taking it with strong water pills (like furosemide) or other antibiotics that affect the kidneys.(34).

Precautions
Tell your doctor if you have any kidney problems before starting treatment. This drug stays in the body longer when the kidneys aren't working well, which can lead to side effects. If you have a history of seizures or brain-related issues, you may need extra monitoring during treatment. Also, let your doctor know about all the medicines you're taking to avoid harmful drug interactions. Regular blood and kidney tests might be done during treatment, especially if it's given for more than a week.

5.In vitro activity
MICs were determined by broth microdilution for ceftazidime, ceftazidime-avibactam, cefepime, cefepime-enmetazobactam, ceftolozane-tazobactam, ertapenem, imipenem, imipenem-relebactam, meropenem, and meropenem-vaborbactam with a range from 0.25 to >16 mg/L, using a customized Sensititre microplate (Thermo Fisher Scientific). As recommended by EUCAST, BLI concentrations were fixed at 4 mg/L for tazobactam, avibactam, and relebactam and at 8 mg/L for avobactam and enmetazobactam. The results were interpreted according to the EUCAST guidelines as updated in 2024 [19]. For cefepime-enmetazobactam, the EUCAST breakpoints released in 2024 for Enterobacteriaceae were used (susceptible for MIC 4 mg/L an resistance for MIC >4 mg/L)

Although the clinical efficacy of cefepime-enmetazobactam demonstrated its relevance as therapy for the treatment of ESBL-producing Enterobacterales when compared with piperacillin-tazobactam [12], its role in the treatment of carbapenem-resistant Gram negatives was not reported yet. Here, we tested the efficacy of cefepime-enmetazobactam against a large collection of carbapenem-resistant Gram-negative isolates (2,212 CRE and CPE, 50 P. aeruginosa and 30 A. baumannii).

Our results confirmed the absence of inhibitory activity of enmetazobactam towards metallo-b-lactamases (mostly NDM and VIM) [8,10].

At the opposite, we e demonstrated that cefepime-enmetazobactam might be considered as a relevant therapeutic option for the treatment of infections caused by OXA-48-producers.

Indeed, since OXA-48-like carbapenemases are unable to hydrolyze ceftazidime, aztreonam or cefepime, a combination with a BLI able to strongly inhibit additional extended-spectrum b-lactamase might be highly relevant. On the 1000 consecutive OXA-48 producers from France, cefepime-enmetazobactam and ceftazidime-avibactam exhibited a similar activity.(35)

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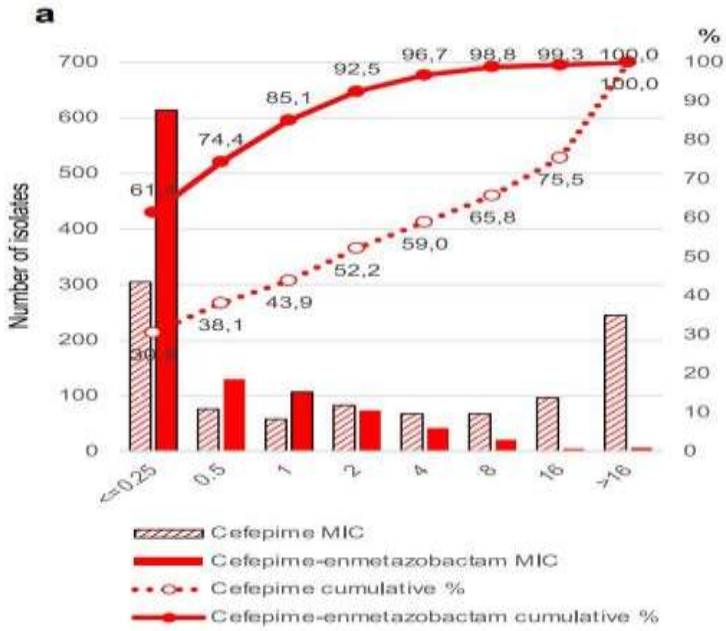

Figure 6. MICs and cumulative MIC distribution of OXA-48 like production Enterobacteriaceae to cefepim - enmetazobactam .(36)

6.ANLYTICAL METHOD

Official method

Table 6. Official method cefepim

Sr no.	Title	Chromatography parameters
1.	IP	**Mobile phase: A** mixture of 94 volume of a solution prepared by dissolving 5.76 g of sodium 1-pentanesulfonate in 2009 mL of water glacial acetic acid and then pH 4.0 with potassium hydroxide and 6 volume of acetonitrile **Column:** stainless steel column porous silica (5 u) **Flow rate :** 2 ML /min **Wave length:** 254 nm
2.	USP	**Mobile phase:** 0.68 mg/ ml of monobasic potassium phosphate in water **Mobile phase B.** Acetonitrile and mobile phase A (1:9% v/v) adjusted with 2% phosphoric acid or 2% potassium hydroxide to a PH of 5.0 % v/v **Mobile phase C:** acetonitrile and solutions A (1:1 v/v) adjusted with 2% phosphoric acid or 2% potassium hydroxide to a PH 5.0 **Column: 5 um packing LI** **Flow rate: 1 ml/ min** **Wavelength: 254 nm**

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Official method cefepim in are a chemical used in
Sodium 1-pentanesulfonate
Potassium hydroxide (36)

Table 7. Cefepim enmetazobactam combination drug in chromatography method (37)

Sr no.	Title	Chromatography parameters
1.	**Liquid chromatography tandem mass spectrometry for the simultaneous quantitation of enmetazobactam and cefepim human plasma**	**Mobile phase A:** ammonium formate in water and acetonitrile **Column:** BEH HILIC column (50 mm× 2.1 mm 1.7 mm) **Flow rate:** lower limit of quantification was 0.05 g/ml for enmetazobactam and 0.5 g/ml for cefepim.

7.OVER DOSE

Patients who receive an overdose should be carefully observed and given supportive treatment. Cefepime and enmetazobactam can be removed by hemodialysis, although no clinical information is available on using hemodialysis to treat Exblifep overdosage. Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, neuromuscular excitability, and nonconvulsive status epilepticus.(38)

8. Use

EXBLIFEP is a combination of cefepime, a cephalosporin antibacterial, and enmetazobactam, a beta-lactamase inhibitor, indicated for the treatment of patients 18 years and older with complicated urinary tract infections (cUTI) including pyelonephritis caused by designated susceptible microorganisms.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of EXBLIFEP and other antibacterial drugs, EXBLIFEP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. (39).

II. CONCLUSION

Cefepime enmetazobactam emerges as a highly promising therapeutic combination addressing the escalating global challenge posed by multi drug resistance gram- negative bacteria, particularly ESBL - producing Enterobacterales and certain carbapenams producing pathogens. rigorous clinical evidence notably from the phase 3 ALLIUM trial demonstrate its superior efficacy compared to severe infections including completed urinary tract infections and conventional therapies such as piperacillin-tazobactam providing a critical alternative for the management of severe infections including complicated urinary tract infections intra abdominal infections.

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