EXBLIFEP- cefepime hydrochloride, enmetazobactam injection, powder, for solution
Allecra Therapeutics SAS

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EXBLIFEP safely and effectively. See full prescribing information for EXBLIFEP.

EXBLIFEP® (cefepime and enmetazobactam) for injection, for intravenous use
Initial U.S. Approval: 2024

INDICATIONS AND USAGE

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. (1.1)
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. (1.2)

DOSAGE AND ADMINISTRATION

- Administer EXBLIFEP 2.5 grams (2 grams cefepime and 0.5 grams enmetazobactam) every 8 hours by intravenous infusion over 2 hours for 7 days to 14 days, in patients 18 years of age and older with an estimated glomerular filtration rate (eGFR) between 60 to 129 mL/min. (2.1)
- Dosage adjustment is recommended in patients with renal impairment who have an eGFR < 60 mL/min or ≥ 130 mL/min. (2.2)

Recommended Dosage of EXBLIFEP Based on Renal Function

eGFR[a] (mL/min)	Recommended Dosage Regimen for EXBLIFEP (cefepime and enmetazobactam)[b]	Dosing Interval and Infusion Duration
Greater than or equal to 130	EXBLIFEP 2.5 grams (2 grams cefepime and 0.5 grams enmetazobactam)	Every 8 hours (4-hour infusion)
90 to 129	EXBLIFEP 2.5 grams (2 grams cefepime and 0.5 grams enmetazobactam)	Every 8 hours (2-hour infusion)
60 to 89	EXBLIFEP 2.5 grams (2 grams cefepime and 0.5 grams enmetazobactam)	Every 8 hours (2-hour infusion)
30 to 59	EXBLIFEP 1.25 grams (1 gram cefepime and 0.25 grams enmetazobactam)	Every 8 hours (2-hour infusion)
15 to 29	EXBLIFEP 1.25 grams (1 gram cefepime and 0.25 grams enmetazobactam)	Every12 hours (2-hour infusion)
Less than 15 or receiving intermittent hemodialysis[c]	Loading dose of EXBLIFEP 1.25 grams (1 gram cefepime and 0.25 grams enmetazobactam) on the first day of treatment, followed by EXBLIFEP 0.625 grams (0.5 grams cefepime and 0.125 grams enmetazobactam)	Every 24 hours (2-hour infusion)

[a] As calculated using the Modification of Diet in Renal Disease (MDRD) formula; [b] The total duration of treatment is for 7 to 14 days; [c] On hemodialysis days, doses should be administered after a hemodialysis session.

- See Full Prescribing Information for instructions for reconstituting supplied dry powder and subsequent required dilution. (2.3)
- See Full Prescribing Information for drug compatibilities. (2.4)

DOSAGE FORMS AND STRENGTHS

EXBLIFEP 2.5 grams (cefepime and enmetazobactam) for injection, is supplied as a sterile powder for reconstitution in single-dose vials containing 2 grams cefepime and 0.5 grams enmetazobactam. (3)

CONTRAINDICATIONS

EXBLIFEP is contraindicated in patients with a history of serious hypersensitivity reactions to the

components of EXBLIFEP (cefepime and enmetazobactam), or other beta-lactam antibacterial drugs. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Hypersensitivity reactions have been reported in patients treated with EXBLIFEP. Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis, have been reported with beta-lactam antibacterial drugs. If an allergic reaction to EXBLIFEP occurs, discontinue the drug and institute appropriate therapy. (5.1)
- Neurotoxicity: Neurotoxicity has been reported during treatment with cefepime, a component of EXBLIFEP. Most cases occurred in patients with renal impairment who did not receive appropriate dosage adjustment of cefepime. If neurotoxicity occurs, discontinue EXBLIFEP and institute appropriate supportive measures. (5.2)
- *Clostridioides difficile*-Associated Diarrhea (CDAD): CDAD has been reported with nearly all systemic antibacterial agents, including EXBLIFEP. Evaluate if diarrhea occurs. (5.3)

ADVERSE REACTIONS

The most frequently reported adverse reactions occurring in ≥5% of patients treated with EXBLIFEP were transaminases increased, increased bilirubin, headache, and phlebitis/infusion site reactions. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Allecra Therapeutics SAS at 1-800-880-1978 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

Geriatric Use: Serious neurologic adverse reactions have occurred in geriatric patients with renal insufficiency given unadjusted doses of cefepime, a component of EXBLIFEP. Care should be taken in dose selection for elderly patients and renal function should be monitored as appropriate. (8.5)
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1. Complicated Urinary Tract Infections, including Pyelonephritis

EXBLIFEP® is indicated for the treatment of patients 18 years of age and older with complicated urinary tract infections (cUTI) including pyelonephritis, caused by the following susceptible microorganisms: *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis,* and *Enterobacter cloacae* complex.

1.2. Usage

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. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2. DOSAGE AND ADMINISTRATION

2.1. Recommended Dosage and 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.

2.2. 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 *[see Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)].* For patients with changing renal function, monitor serum creatinine concentrations and eGFR at least daily and adjust the dosage of EXBLIFEP accordingly *[see Use in Specific Populations (8.6)]*.

Table 1: Recommended Dosage of EXBLIFEP in Patients (18 Years of Age and Older) Based on Renal Function

eGFR[a] (mL/min)	**Recommended Dosage Regimen for EXBLIFEP (cefepime and enmetazobactam)[b]**	**Dosing Interval**	**Infusion Time**
Greater than or equal to 130	EXBLIFEP 2.5 grams (2 grams cefepime and 0.5 grams enmetazobactam)	Every 8 hours	4 hours
90 to 129	EXBLIFEP 2.5 grams (2 grams cefepime and 0.5 grams enmetazobactam)	Every 8 hours	2 hours
60 to 89	EXBLIFEP 2.5 grams (2 grams cefepime and 0.5 grams enmetazobactam)	Every 8 hours	2 hours
30 to 59	EXBLIFEP 1.25 grams (1 gram cefepime and 0.25 grams enmetazobactam)	Every 8 hours	2 hours
15 to 29	EXBLIFEP 1.25 grams (1gram cefepime and 0.25 grams enmetazobactam)	Every 12 hours	2 hours
less than 15 or receiving intermittent hemodialysis[c]	Loading dose of EXBLIFEP 1.25 grams (1 gram cefepime and 0.25 grams enmetazobactam) on the first day of treatment, followed by EXBLIFEP 0.625 grams (0.5 grams cefepime and 0.125 grams enmetazobactam)	Every 24 hours	2 hours

[a] As calculated using the Modification of Diet in Renal Disease (MDRD) formula

[b] The total duration of treatment is for 7 to 14 days.

[c] In patients requiring intermittent hemodialysis, complete the hemodialysis session before the start of EXBLIFEP dosing. Whenever possible, administer cefepime and enmetazobactam at the same time each day.

2.3. Preparation of EXBLIFEP for Intravenous Infusion Administration

Preparation

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.

Table 2: Preparation of EXBLIFEP Doses

EXBLIFEP (cefepime and enmetazobactam) Dose	**Number of Vials to Reconstitute for Further Dilution**	**Volume to Withdraw from Each Reconstituted Vial for Further Dilution**	**Volume of Infusion Bag**
2.5 grams (2 grams cefepime and 0.5 grams enmetazobactam)	1 vial	Entire contents (approximately 13 mL)	250 mL
1.25 grams (1 gram cefepime and 0.25 grams enmetazobactam)	1 vial	Partial contents (6.5 mL)	250 mL
0.625 grams (0.5 grams cefepime and 0.125 grams enmetazobactam)	1 vial	Partial contents (3.3 mL)	250 mL

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.

2.4. Drug Compatibility

EXBLIFEP is compatible with 0.9% Sodium Chloride Injection, 5% Dextrose injection, and 2.5% Dextrose and 0.45% Sodium Chloride.

Compatibility of EXBLIFEP solution for administration with other drugs has not been established.

3. DOSAGE FORMS AND STRENGTHS

EXBLIFEP 2.5 grams (cefepime and enmetazobactam) for injection, is supplied as a white to off-white sterile powder for reconstitution in single-dose vials, containing 2 grams cefepime and 0.5 grams enmetazobactam.

4. CONTRAINDICATIONS

EXBLIFEP is contraindicated in patients with a history of serious hypersensitivity reactions to the components of EXBLIFEP (cefepime and enmetazobactam) or other beta-lactam antibacterial drugs *[see Warnings and Precautions (5.1)]*.

5. WARNINGS AND PRECAUTIONS

5.1. Hypersensitivity Reactions

Hypersensitivity reactions have been reported in patients treated with EXBLIFEP *[see Adverse Reactions (6.1)]*. Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis, and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs *[see Contraindications (4)]*. Before therapy with EXBLIFEP is instituted, carefully inquire about previous hypersensitivity reactions to cefepime, cephalosporins, penicillins, or other beta-lactams because cross-hypersensitivity among beta-lactam antibacterial drugs has been reported. If an allergic reaction to EXBLIFEP occurs, discontinue the drug and institute appropriate supportive measures.

5.2. Neurotoxicity

Neurotoxicity has been reported during treatment with cefepime, a component of EXBLIFEP, including life-threatening or fatal occurrences of the following: encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), aphasia, myoclonus, seizures, and nonconvulsive status epilepticus *[see Adverse Reactions (6.2)]*. Most cases occurred in patients with renal impairment who did not receive appropriate dosage adjustment. However, some cases of neurotoxicity occurred in patients receiving a dosage adjustment appropriate for their degree of renal impairment. In the majority of cases, symptoms of neurotoxicity were reversible and resolved after discontinuation of cefepime and/or after hemodialysis. If neurotoxicity associated with EXBLIFEP therapy occurs, discontinue EXBLIFEP and institute appropriate supportive measures.

5.3. *Clostridioides difficile*-associated Diarrhea

Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including EXBLIFEP, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial

drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.4. Positive Direct Coombs' Tests

Positive direct Coombs' tests with or without hemolysis have been reported during treatment with cefepime, a component of EXBLIFEP. In patients who develop hemolytic anemia, discontinue the drug and institute appropriate therapy. Positive Coombs' test may be observed in newborns whose mothers have received cephalosporin antibacterial drugs before parturition.

5.5. Prolonged Prothrombin Time

Many cephalosporins, including cefepime, a component of EXBLIFEP, have been associated with a decrease in prothrombin activity. Those at risk of developing a prolonged prothrombin time include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk, and exogenous vitamin K administered as indicated.

5.6. Development of Drug-Resistant Bacteria

Prescribing EXBLIFEP in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

5.7. Interactions with Urine Glucose Testing

The administration of cefepime, a component of EXBLIFEP, may result in a false-positive reaction for glucose in the urine when using some methods (e.g., Clinitest™ tablets) *[see Drug Interactions (7.3)]*.

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the Warnings and Precautions section:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Neurotoxicity *[see Warnings and Precautions (*5.2*)]*
- *Clostridioides difficile*-associated Diarrhea *[see Warnings and Precautions (5.3)]*

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

EXBLIFEP was evaluated in a phase 3 comparator-controlled clinical trial in cUTI, including pyelonephritis (also referred to as Trial 1), which included 516 patients treated

with EXBLIFEP 2.5 grams (2 grams cefepime and 0.5 grams enmetazobactam) every 8 hours infused over 2 hours, and 518 patients treated with the comparator piperacillin/tazobactam 4.5 grams (4 grams piperacillin and 0.5 grams tazobactam) every 8 hours infused over 2 hours. No switch to oral therapy was permitted. Patients were to receive treatment for 7 days; those with baseline bacteremia could receive up to 14 days of treatment. The mean duration of therapy was 8 days in both treatment groups.

The mean age of patients treated with EXBLIFEP was 55 years and 40% of patients were 65 years of age or older. Patients were predominantly female (54%) and White (94%). Most patients were enrolled in Europe (93%).

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% (10/518) of patients receiving piperacillin/tazobactam. The most common adverse reactions leading to discontinuation of EXBLIFEP were hypersensitivity, nausea, and increased transaminases, each 0.4% (2/516). The other adverse reactions resulting in discontinuation of EXBLIFEP were abdominal pain, bacterial infection, chest pain, eructation, fungal infection, gastroenteritis, headache, insomnia, pneumonia, restlessness, and urinary retention, each 0.2% (1/516). Death was reported in 3 (0.6%) patients who received EXBLIFEP and in 3 (0.6%) patients who received piperacillin/tazobactam.

Common Adverse Reactions

The most frequently reported adverse reactions (5% or greater) in patients receiving EXBLIFEP were transaminases increased, bilirubin increased, headache, and phlebitis/infusion site reactions. Table 3 lists selected adverse reactions occurring in 1% or greater of patients receiving EXBLIFEP in Trial 1.

Table 3: Selected Adverse Reactions Occurring in 1% or Greater of cUTI Patients Receiving EXBLIFEP in Trial 1

Adverse Reactions	**EXBLIFEP (N=516) N (%)**	**Piperacillin/Tazobactam (N=518) N (%)**
Transaminases increased[a]	101 (20)	103 (20)
Bilirubin increased[b]	36 (7)	21 (4)
Headache[c]	26 (5)	12 (2)
Phlebitis/Infusion site reactions[d]	24 (5)	2 (<1)
Diarrhea	21 (4)	26 (5)
Anemia[e]	16 (3)	16 (3)
Hypersensitivity[f]	10 (2)	3 (<1)
Vomiting	9 (2)	6 (1)
Nausea	6 (1)	3 (<1)

[a] Transaminases increased includes alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, hepatic enzyme increased, liver function test increased, transaminases increased, and hypertransaminasemia.

[b] Bilirubin increased includes 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 groups.

Other Adverse Reactions Associated With EXBLIFEP

The following selected adverse reactions were reported in EXBLIFEP-treated patients at a rate of less than 1% in Trial 1:

Blood and lymphatic system disorders: eosinophilia, partial thromboplastin time prolonged, thrombocytopenia

Gastrointestinal Disorders: eructation

Infections and Infestations: Clostridioides difficile colitis

Laboratory Investigations: alkaline phosphatase increased

Vascular Disorders: epistaxis

Metabolism and nutrition disorders: hypocalcemia, hyperkalemia

Nervous System Disorders: dizziness

Psychiatric Disorders: restlessness

Renal and urinary disorders: blood urea nitrogen increased, blood creatinine increased

Other Adverse Reactions Associated with Cefepime in Other Clinical Trials

Additionally, adverse reactions reported with cefepime alone in other clinical trials that were not reported in the EXBLIFEP-treated patients in Trial 1 are listed below:

Infections and infestations: oral candidiasis, vaginitis

Blood and lymphatic system disorders: Coombs' test positive (without hemolysis), prothrombin time prolonged, leukopenia, neutropenia

General disorders and administration site conditions: pyrexia,

Laboratory Investigations: increased calcium, increased phosphorus, decreased phosphorus

Laboratory Changes Associated with EXBLIFEP

The incidence of patients with increases in ALT, AST, or total bilirubin laboratory values greater than specified levels is presented in Table 4.

Table 4: Selected Laboratory Abnormalities Exceeding Specified Levels in Trial 1

Laboratory Parameter	**EXBLIFEP (N=516) n/N_W (%)**	**Piperacillin/Tazobactam (N=518) n/N_W (%)**
Alanine aminotransferase		

(U/L)		
>3x ULN	14/514 (3)	6/515 (1)
Aspartate aminotransferase (U/L)		
>3x ULN	11/514 (2)	6/515 (1)
Bilirubin, total (mg/dL)		
>2x ULN	2/514 (<1)	7/515 (1)

N, total number of patients in treatment arm; N_W, number of patients with baseline lab data available in each baseline toxicity subgroup; n, number of patients meeting criteria; ULN, Upper Limit of Normal.

6.2. Postmarketing Experience

The following adverse reactions and altered laboratory tests have been identified during post-approval use of cefepime or other cephalosporin-class antibacterial drugs. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Blood and lymphatic system disorders: Agranulocytosis, aplastic anemia, hemolytic anemia, pancytopenia

Nervous system disorders: Encephalopathy (including disturbance of consciousness, hallucinations, stupor, and coma), aphasia, myoclonus, seizures, and nonconvulsive status epilepticus

Immune system disorders: Anaphylaxis including anaphylactic shock, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis

Hepatobiliary disorders: Hepatic dysfunction including cholestasis

Renal and urinary disorders: Renal dysfunction, toxic nephropathy

Vascular disorders: Hemorrhage

7. DRUG INTERACTIONS

7.1. Aminoglycosides

Monitor renal function if aminoglycosides are to be administered with EXBLIFEP because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibacterial drugs.

7.2. Diuretics

Monitor renal function when EXBLIFEP is concomitantly administered with potent diuretics. Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide.

7.3. Drug/Laboratory Test Interactions

It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used in patients using EXBLIFEP. The administration of EXBLIFEP may result in a false-

positive reaction for glucose in the urine with certain methods *[see Warning and Precautions (5.7)]*.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

There are no available data with the use of EXBLIFEP, or enmetazobactam during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Available data from published observational studies and case reports over several decades with cephalosporin use, including cefepime, in pregnant women have not established drug-associated risks of major birth defects, miscarriage or adverse maternal or fetal outcomes (*see Data*).

Cefepime

Cefepime was not associated with adverse developmental outcomes in rats, mice, or rabbits when administered parenterally during organogenesis. The doses used in these studies were 1.6 (rats), approximately equal to (mice), and 0.3 times (rabbits) the maximum recommended human dose (MRHD) (*see Data*).

Enmetazobactam

Intravenous administration of enmetazobactam to pregnant rats and rabbits during organogenesis was associated with maternal toxicity and reduced fetal weights, but not fetal malformations at approximately 7 times and 11 times, respectively, the MRHD (1.5 g/day).

Intravenous administration of enmetazobactam to pregnant rats during organogenesis through lactation resulted in reduction of maternal body weights and reduced fetal body weights and delayed pinna detachment in first-generation offspring in the absence of any other adverse effects on the survival, growth, and development of first- and second-generation offspring at exposures 7-times the MRHD (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Cefepime

While available studies cannot definitively establish the absence of risk, published data from case-control studies and case reports over several decades have not identified an association with cephalosporin use, including cefepime, during pregnancy and major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups.

Animal Data

Cefepime

Cefepime was not embryocidal and did not cause fetal malformations when administered parenterally during the period of organogenesis to rats at doses up to 1000 mg/kg/day, to mice at doses up to 1200 mg/kg/day, or to rabbits at doses up to 100 mg/kg/day. These doses are 1.6 times (rats), approximately equal to (mice), and 0.3 times (rabbits) the maximum recommended clinical dose based on body surface area.

Enmetazobactam

Enmetazobactam was administered to pregnant rats in intravenous doses of 125, 250, and 500 mg/kg/day during the period of organogenesis from Gestation Day (GD) 6 through GD 17. Maternal weight gain was reduced at 500 mg/kg/day (approximately 7 times the MRHD based on plasma AUC comparison). No fetal malformations were observed with any dose of enmetazobactam, but fetal weights were reduced in the high-dose group. The dose at which no maternal or fetal toxicity occurred was 250 mg/kg/day (approximately 3 times the MRHD based on plasma AUC comparison).

Enmetazobactam was administered intravenously to pregnant rabbits in doses of 50, 150, and 300 mg/kg/day during the period of organogenesis from GD 7 through GD 19. Maternal body weight gains were reduced in the mid- and high-dose groups (approximately 11 and 25 times the MRHD respectively based on plasma AUC comparison). No fetal malformations were observed, but the mean values for total litter weights and fetal weights were decreased in the mid- and high-dose groups, and mean placental weights were decreased in the high-dose group. The dose at which no maternal or fetal toxicity occurred was 50 mg/kg/day (approximately 3-times the MRHD based on plasma AUC comparison).

In a pre-postnatal study, enmetazobactam was administered intravenously to pregnant rats from GD 6 through the lactation period until Lactation Day 20 in maternal doses of 125, 250, and 500 mg/kg/day. Maternal body weights and the body weights of first-generation offspring were reduced, and pinna detachment in first-generation off-spring was delayed with the maternal dose of 500 mg/kg/day (approximately 7-times the MRHD based on plasma AUC comparison). No other adverse effects on the survival, development, behavior, or reproduction of first-generation offspring occurred with any of the maternal enmetazobactam doses up to 500 mg/kg/day. The survival, growth and development of second-generation offspring were not adversely affected by maternal enmetazobactam doses up to 500 mg/kg/day (approximately 7-times the MRHD based on plasma AUC comparison). The dose at which no maternal toxicity or toxicity in first-generation offspring occurred was 250 mg/kg/day (approximately 3-times the MRHD based on plasma AUC comparison). No adverse effects occurred in second-generation offspring at 500 mg/kg/day (approximately 7-times the MRHD based on plasma AUC comparison).

8.2. Lactation

Risk Summary

Cefepime

Cefepime is present in human breast milk at low concentrations (approximately 0.5 mcg/mL) following a single intravenous dose of 1000 mg. A nursing infant consuming

approximately 1000 mL of human milk per day would receive approximately 0.5 mg of cefepime per day *(see Data)*.

Enmetazobactam

Enmetazobactam was present in the milk of lactating rats *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. There is no information regarding the effects of cefepime, enmetazobactam or their combination on the breastfed infant or on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EXBLIFEP and any potential adverse effects on the breastfed child from EXBLIFEP or from the underlying maternal condition.

Data

Human Data

Cefepime

A pharmacokinetic study was conducted in 9 healthy lactating women to evaluate the concentrations of cefepime in plasma and breast milk following a single intravenous dose of 1000 mg. The mean breast milk concentrations of cefepime during the first 8 hours post-dose were approximately 0.5 mcg/mL and then declined and became undetectable between 12- and 24-hours post-dose. The mean cumulative breast milk excretion of cefepime over 24 hours was 0.01% of the administered dose. The pharmacokinetics of cefepime are similar between lactating and non-lactating women.

Animal Data

Enmetazobactam

In a pharmacokinetic study in rats intended to assess the potential for enmetazobactam secretion into milk, 5 pregnant rats were administered 500 mg/kg/day enmetazobactam by intravenous bolus from Gestation Day (GD) 6 through the day of birth and the subsequent lactation period until Lactation Day (LD) 20. On LD 14, lactation milk was collected 30 minutes after dosing from the 5 maternal rats, and enmetazobactam was measured. Concentrations of enmetazobactam in rat milk ranged from 34 to 317 mcg/ml which is approximately equivalent to 2.6% to 24% of the highest plasma concentrations. The concentration of enmetazobactam in animal milk does not necessarily predict the concentration of drug in human milk.

8.4. Pediatric Use

The safety and effectiveness of EXBLIFEP in pediatric patients (younger than 18 years of age) have not been established.

8.5. Geriatric Use

Of the 516 patients treated with EXBLIFEP in the cUTI trial (Trial 1), 204 (40%) patients were 65 years of age and older, while 78 (15%) patients were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger adult patients, and other reported clinical experience has not identified differences in responses between the elderly and younger adult patients.

Serious neurologic adverse reactions have occurred in geriatric patients with renal

insufficiency given unadjusted doses of cefepime, a component of EXBLIFEP including life-threatening or fatal occurrences of the following: encephalopathy, myoclonus, and seizures *[see Warnings and Precautions (5.2)* and *Adverse Reactions (6.2)]*.

No dosage adjustment based on age is required. EXBLIFEP is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored as appropriate. Dosage adjustment for elderly patients should be based on renal function. *[see Dosage and Administration (2.2), Use in Specific Populations (8.6),* and *Clinical Pharmacology (12.3)*.

8.6. Renal Impairment

Cefepime and enmetazobactam, the components of EXBLIFEP, are primarily renally excreted. Plasma exposures of both cefepime and enmetazobactam increase with decreasing renal function, therefore dosage adjustments are recommended to compensate for the slower rate of renal clearance in patients with eGFR less than 60 mL/min *[see Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)]*.

In patients with eGFR greater than or equal to 130 mL/min, plasma exposures of cefepime and enmetazobactam are decreased. Therefore, dosage adjustments are recommended to compensate for the higher rate of renal clearance in these patients *[see Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)]*.

Both cefepime and enmetazobactam are hemodialyzable; thus, EXBLIFEP should be administered after intermittent hemodialysis on hemodialysis days *[see Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)]*.

Monitor renal function regularly and adjust the dosage of EXBLIFEP accordingly as renal function may change during the course of therapy.

10. OVERDOSAGE

Patients who receive an overdose should be carefully observed and given supportive treatment.

Cefepime and enmetazobactam can be removed by hemodialysis *[see Clinical Pharmacology (12.3)]*. No clinical information is available on the use of 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 *[see Warnings and Precautions (5.2), Adverse Reactions (6.2),* and *Dosage and Administration (2.2)]*.

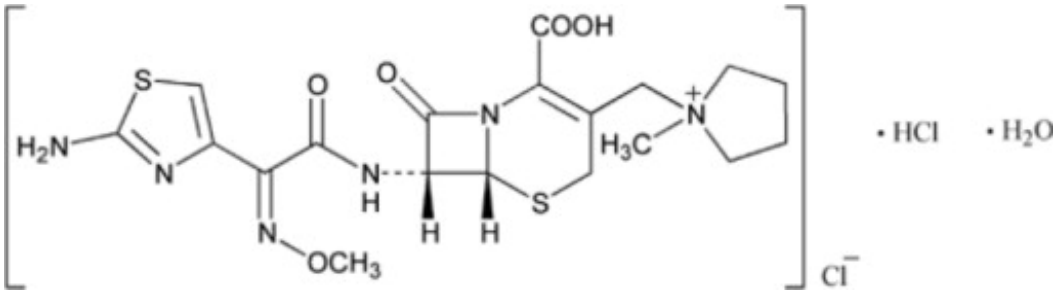
11. DESCRIPTION

EXBLIFEP (cefepime and enmetazobactam) for injection is a combination product that contains cefepime, a cephalosporin antibacterial drug, and enmetazobactam, a beta-lactamase inhibitor, for intravenous administration.

Cefepime, present as cefepime hydrochloride monohydrate, is a white to pale yellow

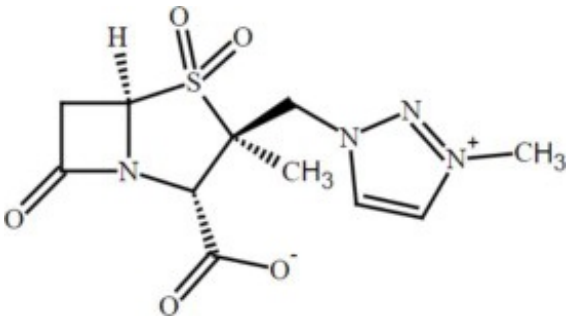
powder. The chemical name for cefepime is (6R,7R,Z)-7-(2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido)-3-((1-methylpyrrolidinium-1-yl)methyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate. The empirical formula of cefepime hydrochloride monohydrate is $C_{19}H_{24}N_6O_5S_2 \cdot 2HCl \cdot H_2O$, the molecular weight is 571.50, and its chemical structure is:

Figure 1: Structure of Cefepime



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 empirical formula is C11H14N4O5S and its chemical structure is:

Figure 2: Structure of Enmetazobactam



EXBLIFEP 2.5 grams (cefepime and enmetazobactam) for injection is supplied as a white to off-white sterile powder for reconstitution. Each vial contains 2 grams of cefepime (equivalent to 2.3 g of cefepime hydrochloride), 0.5 grams of enmetazobactam, and 1.414 grams of L-arginine.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

EXBLIFEP is an antibacterial drug *[see Microbiology (12.4)]*.

12.2. Pharmacodynamics

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 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.

12.3. 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

Pharmacokinetic Parameters	**Cefepime**	**Enmetazobactam**
Exposure		
C_{max} (µg/mL)[1]	99.8 (26.4)	19.8 (6.3)
AUC_{last} (µg•h/mL)[1]	379.5 (123.3)	75.3 (30.8)
Distribution		
% Bound to human plasma protein	20%	Negligible
Vss (L)	20.02 (6.44)	25.26 (9.97)
Proportionality	Exposure approximately proportional to dose following IV administration	
Accumulation	Similar pharmacokinetics following single and multiple dosing	
Elimination		
CL (L/h)	5.8 (1.9)	7.6 (2.9)
$T_{1/2}$ (h)	2.7 (1.1)	2.6 (1.1)
Metabolism[2]	Minimally metabolized	
Excretion		
Major route of elimination	Renal	
% Excreted unchanged in urine	85%	90%

[1] Pharmacokinetic parameters are presented at steady state (Day 7) in patients with cUTI and eGFR greater than or equal to 60 mL/min at a dosage of 2 g cefepime and 0.5 g enmetazobactam every 8 hours

[2] Approximately 7% of the cefepime dose is metabolized to N-methylpyrrolidine (NMP) which is rapidly converted to the N-oxide (NMP-N-oxide)

$AUC_{0\text{-last}}$ = area under the plasma concentration time curve from time of dosing to the last measurable concentration; CL = clearance; C_{max} = maximum concentration; SD = standard deviation, $T_{1/2}$ = terminal half-life; Vss = volume of distribution at steady state

Specific Populations

No clinically significant differences in the pharmacokinetics of cefepime or enmetazobactam were observed based on age (18 – 94 years), gender, or weight (45 – 135 kg). There was insufficient information to evaluate the effect of race on the pharmacokinetics of cefepime or enmetazobactam.

Patients with Renal Impairment

In a single-dose trial evaluating the effect of renal impairment on the pharmacokinetics of cefepime and enmetazobactam, dose-normalized systemic exposures of cefepime and enmetazobactam were higher at all levels of renal impairment compared to healthy subjects with CLcr greater than or equal to 90 mL/min (Table 6). In subjects with creatinine clearance (CLcr) < 15 mL/min on hemodialysis, the fraction of the dose removed by hemodialysis was 0.30 and 0.35 for cefepime and enmetazobactam, respectively *[see Dosage and Administration (2.2)* and *Use in Specific Populations (8.6)].*

Table 6: Dose Normalized Fold AUC Increase in Subjects with Renal Impairment Compared to Subjects with Creatinine Clearance (CLcr) ≥ 90 mL/min

Pharmacokinetic Parameters	**Cefepime**	**Enmetazobactam**
≥60 to <90	1.9	1.8
≥30 to <60	3	3
≥15 to <30	5.3	5.3
<15	12	11

Patients with eGFR 130 mL/min or Greater

Increased cefepime and enmetazobactam clearance have been observed in patients with eGFR of 130 mL/min or greater. An EXBLIFEP (2 g cefepime and 0.5 g enmetazobactam) dose every 8 h infused over 4 hours provided cefepime and enmetazobactam exposures comparable to those in patients with eGFR 90 to 129 mL/min who received EXBLIFEP (2 g cefepime and 0.5 g enmetazobactam) dose every 8 h over 2 hours *[see Dosage and Administration (2.2)* and *Use in Specific Populations (8.6)].*

Patients with Hepatic Impairment

Cefepime and enmetazobactam are primarily cleared renally; therefore, hepatic impairment is not likely to have a significant effect on cefepime or enmetazobactam exposures.

Drug Interactions

Clinical Studies

No drug-drug interactions were observed among cefepime, enmetazobactam and piperacillin in a clinical study in healthy subjects.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

Cytochrome P450 (CYP) Enzymes: At therapeutic plasma concentrations, enmetazobactam does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9,

CYP2C19, CYP2D6, or CYP3A4. Enmetazobactam inhibits CYP2E1. Enmetazobactam does not induce CYP1A2, CYP2B6, or CYP3A4.

Membrane Transporter Systems: Enmetazobactam is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, BSEP, OAT1, OAT3, MATE1, or MATE2-K. *In vitro* data also indicated that enmetazobactam did not inhibit P-gp, MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1, OAT3, BSEP, MRP3, MRP4 and NTCP.

No *in vitro* CYP450 enzyme or membrane transporter drug interaction studies were conducted with cefepime.

12.4. Microbiology

Mechanism of Action

The cefepime component of EXBLIFEP is a cephalosporin antibacterial drug. The bactericidal action of cefepime results from the inhibition of cell wall synthesis. Cefepime penetrates the cell wall of most gram-positive and gram-negative bacteria to bind penicillin-binding protein (PBP) targets. Cefepime is stable to hydrolysis by some beta-lactamases, including penicillinases and cephalosporinases produced by gram-negative and gram-positive bacteria, with the exception of extended spectrum beta-lactamases (ESBL), some oxacillinases, and carbapenem hydrolyzing beta-lactamases.

The enmetazobactam component of EXBLIFEP is a beta-lactamase inhibitor that protects cefepime from degradation by certain serine beta-lactamases such as ESBL.

Resistance

Mechanisms of resistance to EXBLIFEP may include the production of beta-lactamases that are not inhibited by enmetazobactam, modification of PBPs by target alteration, overexpression of efflux pumps, and outer membrane porin mutations.

Clinical isolates may produce multiple beta-lactamases, express varying levels of beta-lactamases, or have amino acid sequence variations, and other resistance mechanisms that have not been identified.

Culture and susceptibility information and local epidemiology should be considered in selecting or modifying antibacterial therapy.

Cefepime-enmetazobactam demonstrated in vitro activity against Enterobacterales in the presence of some beta-lactamases and extended-spectrum beta-lactamases (ESBL) of the following groups: CTX-M, SHV, TEM, and VEB. EXBLIFEP is not active against bacteria that produce KPC, metallo-beta-lactamases or some oxacillinases (OXA). Cefepime is inherently stable to hydrolysis by some AmpC cephalosporinases and OXA-48.

In the Phase 3 cUTI trial with EXBLIFEP, some isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae* species complex, *Citrobacter braakii*, *Citrobacter freundii*, and *Proteus mirabilis*, that produced beta-lactamases had a minimum inhibitory concentration ≤4 µg/mL for EXBLIFEP. These isolates carried genes for one or more beta-lactamases of the following enzyme groups: CTX-M, TEM, SHV, VEB, CMY, and OXA-48.

In the Phase 3 cUTI trial with EXBLIFEP, some beta-lactamases were also produced by isolates of *K. pneumoniae* and an isolate of *E. cloacae* that had a minimum inhibitory concentration ≥16 mcg/mL for EXBLIFEP. The *K. pneumoniae* isolates contained genes for NDM-1, OXA-48, or KPC-3 along with CTX-M, CMY, TEM, and/or SHV. The *E. cloacae*

isolate encoded CTX-M.

No cross-resistance with other non-beta-lactam classes of antimicrobials has been identified. Some isolates resistant to carbapenems and to cephalosporins may be susceptible to EXBLIFEP.

Interaction with Other Antimicrobials

In vitro synergy studies did not demonstrate antagonism between EXBLIFEP and azithromycin, aztreonam, ceftazidime-avibactam, clindamycin, daptomycin, doxycycline, levofloxacin, linezolid, meropenem, metronidazole, trimethoprim-sulfamethoxazole, or vancomycin.

Activity against Cefepime Non-susceptible Bacteria in Animal Infection Models

Enmetazobactam restored activity of cefepime in animal models of infection (e.g., mouse thigh infection, urinary tract infection, pulmonary infection and sepsis) caused by cefepime-resistant, ESBL-producing (e.g., CTX-M, SHV, TEM) Enterobacterales.

Antimicrobial Activity

EXBLIFEP has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections *[see Indications and Usage (1.1)]*.

Gram-negative bacteria:
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Proteus mirabilis*
- *Enterobacter cloacae* complex

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for EXBLIFEP against isolates of similar genus or organism group. However, the efficacy of EXBLIFEP in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials. Gram-negative bacteria:
- *Citrobacter freundii*
- *Klebsiella aerogenes*
- *Klebsiella oxytoca*
- *Providencia stuartii*
- *Providencia rettgeri*
- *Serratia marcescens*

Susceptibility Test Methods

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term carcinogenicity studies have not been performed with cefepime or enmetazobactam.

Mutagenesis

Cefepime

In chromosomal aberration studies, cefepime was positive for clastogenicity in primary human lymphocytes, but negative in Chinese hamster ovary cells. In other in vitro assays (bacterial and mammalian cell mutation, DNA repair in primary rat hepatocytes, and sister chromatid exchange in human lymphocytes), cefepime was negative for genotoxic effects. Moreover, in vivo assessments of cefepime in mice (2 chromosomal aberration and 2 micronucleus studies) were negative for clastogenicity.

Enmetazobactam

Enmetazobactam was negative for genetic toxicity in vitro in a bacterial reverse mutation assay and a chromosomal aberration assay in Chinese Hamster ovary cells, and in vivo in a mouse micronucleus assay in bone marrow cells.

Impairment of Fertility

Cefepime

No untoward effects on fertility were observed in rats when cefepime was administered subcutaneously at doses up to 1000 mg/kg/day (1.6 times the recommended maximum human dose calculated on a mg/m^2 basis).

Enmetazobactam

In male and female fertility studies in rats, enmetazobactam was administered intravenously in doses of 125, 250, and 500 mg/kg/day in males for 28 days before mating and for 14 days before the start of the mating period, throughout the mating period, and until Gestation Day (GD) 7 in females. Enmetazobactam had no adverse effect on fertility in either sex and no effect on early embryonic development in female rats at doses up to 500 mg/kg/day, (approximately 7 times in males and 8 times in females the maximum recommended human dose (1.5 g/day) based on plasma AUC comparison).

14. CLINICAL STUDIES

14.1. Complicated Urinary Tract Infections, including Pyelonephritis

A total of 1041 adults with cUTI, including pyelonephritis, were randomized in a 1:1 ratio into in a multinational, double blind, noninferiority trial (Trial 1, NCT03687255), comparing EXBLIFEP (2 grams cefepime and 0.5 grams enmetazobactam) to piperacillin/tazobactam (4 grams piperacillin and 0.5 grams tazobactam) both administered intravenously every 8 hours (infused over 2 hours) for 7 days, or up to 14 days for patients with concurrent bacteremia. No switch from IV to oral antibacterial therapy was permitted.

The microbiological modified intent-to-treat population (mMITT) was the primary efficacy analysis population and included all randomized patients who received any study drug

and had at least 1 baseline gram-negative pathogen ≥10^5 colony-forming-units (CFU)/mL in urine culture or the same pathogen in blood and urine cultures that is not resistant to cefepime/enmetazobactam or piperacillin/tazobactam (defined as MIC ≤ 8/8 mcg/mL or MIC ≤ 64/4 mcg/mL, respectively). A total of 345 and 333 patients were included in the mMITT population in EXBLIFEP and piperacillin/tazobactam treatment groups, respectively.

Patient demographic and baseline characteristics were balanced between treatment groups in the mMITT population. Approximately 95% of patients were Caucasian and 60% were female in both treatment groups. The mean age was 54 years with 38% and 31% of patients greater than 65 years of age in the EXBLIFEP and piperacillin/tazobactam treatment groups, respectively. Mean body mass index was approximately 26.5 kg/m^2 in both treatment groups. Concomitant bacteremia was identified in 38 (11%) and 28 (8%) patients at baseline in the EXBLIFEP and piperacillin/tazobactam treatment groups, respectively. The proportion of patients with diabetes mellitus at baseline was 16% and 12% in the EXBLIFEP and piperacillin/tazobactam treatment groups, respectively. The majority of patients (93%) were enrolled from Europe. Overall, in both treatment groups, 51% of patients had pyelonephritis and 49% had cUTI, with 27% and 22% of patients having a non-removable and removable source of infection, respectively. Mean duration of treatment in both treatment groups was 8 days.

EXBLIFEP demonstrated efficacy with regard to composite response, defined as clinical cure and microbiological response, at the Test of Cure (TOC) visit (7 days after the end of treatment) in the mMITT population as shown in Table 7. Clinical cure was defined as the complete resolution (or return to premorbid state) of the baseline signs and symptoms of cUTI or pyelonephritis that were present at Screening (and no new urinary symptoms or worsening of symptoms). Microbiological response was defined as the baseline qualifying Gram-negative pathogen(s) reduced to <10^3 colony-forming units/mL in urine culture and a negative blood culture for a Gram-negative pathogen that was identified as a uropathogen (if repeated after positive baseline blood culture).

Table 7: Composite Response (Clinical Cure, and Microbiological Response) Rates at TOC in Trial 1 of cUTI Including Pyelonephritis (mMITT Population)

Response at the TOC visit	EXBLIFEP n/N (%)	Piperacillin/ Tazobactam n/N (%)	Difference (%) (95% CI)*
Composite Response (Clinical Cure and Microbiological Response)	273/345 (79.1)	196/333 (58.9)	21.2 (14.3, 27.9)
Clinical Cure	319/345 (92.5)	296/333 (88.9)	3.5 (-1.0, 8.0)
Microbiological Response	286/345 (82.9)	216/333 (64.9)	19.0 (12.3, 25.4)

CI = confidence interval.
* The 95% CI was based on the stratified Newcombe method.

Composite response in patients with bacteremia at baseline was achieved in 27/38 (71%) patients in the EXBLIFEP group and 14/28 (50%) patients in the piperacillin/tazobactam group at the TOC visit in the mMITT population.

Composite response (microbiological and clinical cure) rates by pathogen for the m-MITT

population are presented in Table 8.

Table 8: Composite Response (Microbiological Response and Clinical Cure) Rates at TOC by Pathogen in Trial 1 of cUTI Including Pyelonephritis (mMITT Population)

Gram-negative Group or Pathogen	EXBLIFEP n/N (%)	Piperacillin/Tazobactam n/N (%)
Escherichia coli	220/264 (83)	151/254 (59)
Klebsiella pneumoniae	23/34 (68)	18/32 (56)
Pseudomonas aeruginosa	4/13 (31)	4/11 (36)
Proteus mirabilis	15/19 (79)	10/19 (53)
Enterobacter cloacae complex	6/7 (86)	1/3 (33)

In a subset of the *E. coli* and *K. pneumoniae* isolates, genotypic testing identified certain ESBL groups (e.g., TEM, CTX-M, SHV and OXA) in both treatment groups of the cUTI Trial 1. The proportion of patients with composite response at TOC was 56/76 (74%) and 34/66 (52%) in the EXBLIFEP group, and the piperacillin/tazobactam group, respectively, in patients with ESBL- producing bacteria at baseline.

A sensitivity analysis where patients with organisms resistant to piperacillin/tazobactam, according to the current FDA breakpoints (defined as MIC >16/4 mcg/mL for Enterobacterales and >64/4 mcg/mL for *P. aeruginosa*) and one patient with *Stenotrophomonas maltophilia* were excluded from the mMITT population, demonstrated similar efficacy results as in the mMITT population.

16. HOW SUPPLIED/STORAGE AND HANDLING

EXBLIFEP 2.5 grams (cefepime and enmetazobactam) for injection is supplied as a white to off-white sterile powder for reconstitution in single-dose, clear glass vials sealed with a rubber stopper (not made with natural rubber latex) and an aluminum overseal. Each vial is supplied in cartons of 10 vials (NDC 83289-101-02).

Each vial contains 2 grams of cefepime and 0.5 grams of enmetazobactam.

Store EXBLIFEP vials refrigerated at 2°C to 8°C (36°F to 46°F); excursions are permitted to 15°C to 25°C (59°F to 77°F) [see USP, Controlled Room Temperature (CRT)]. Keep the vials in the outer carton to protect from light.

Storage conditions for reconstituted and diluted solutions of EXBLIFEP for injection are described in another section of labeling *[see Dosage and Administration (2.3)].*

17. PATIENT COUNSELING INFORMATION

Serious Allergic Reactions

Advise patients that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. Advise patients to discontinue EXBLIFEP and seek immediate medical attention if allergic reactions occur *[see Warnings and Precautions (5.1)]*.

Neurotoxicity

Advise patients of neurological adverse reactions that could occur with EXBLIFEP use. Instruct patients or their caregivers to inform their healthcare provider at once of any neurological signs and symptoms, including encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), aphasia (disturbance of speaking and understanding spoken and written language), myoclonus, seizures and nonconvulsive status epilepticus *[see Warnings and Precautions (5.2)]*.

Potentially Serious Diarrhea

Diarrhea is a common problem caused by antibacterial drugs, which usually ends when the antibacterial drug is discontinued. Inform patient that they may develop watery and bloody stools (with or without stomach cramps and fever) during treatment and as late as two or more months after having taken the last dose of the antibacterial drug. Inform patients that they should contact their physician as soon as possible if this occurs *[see Warnings and Precautions (5.3)]*.

Antibacterial Resistance

Counsel patients that antibacterial drugs, including EXBLIFEP, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). Patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed *[see Warnings and Precautions (5.6)]*.

Manufactured for: Allecra Therapeutics SAS, 68300 Saint Louis, France

Principal Display Panel – 2.5 g Carton Label

NDC: 83289-101-02

10 single-dose Vials

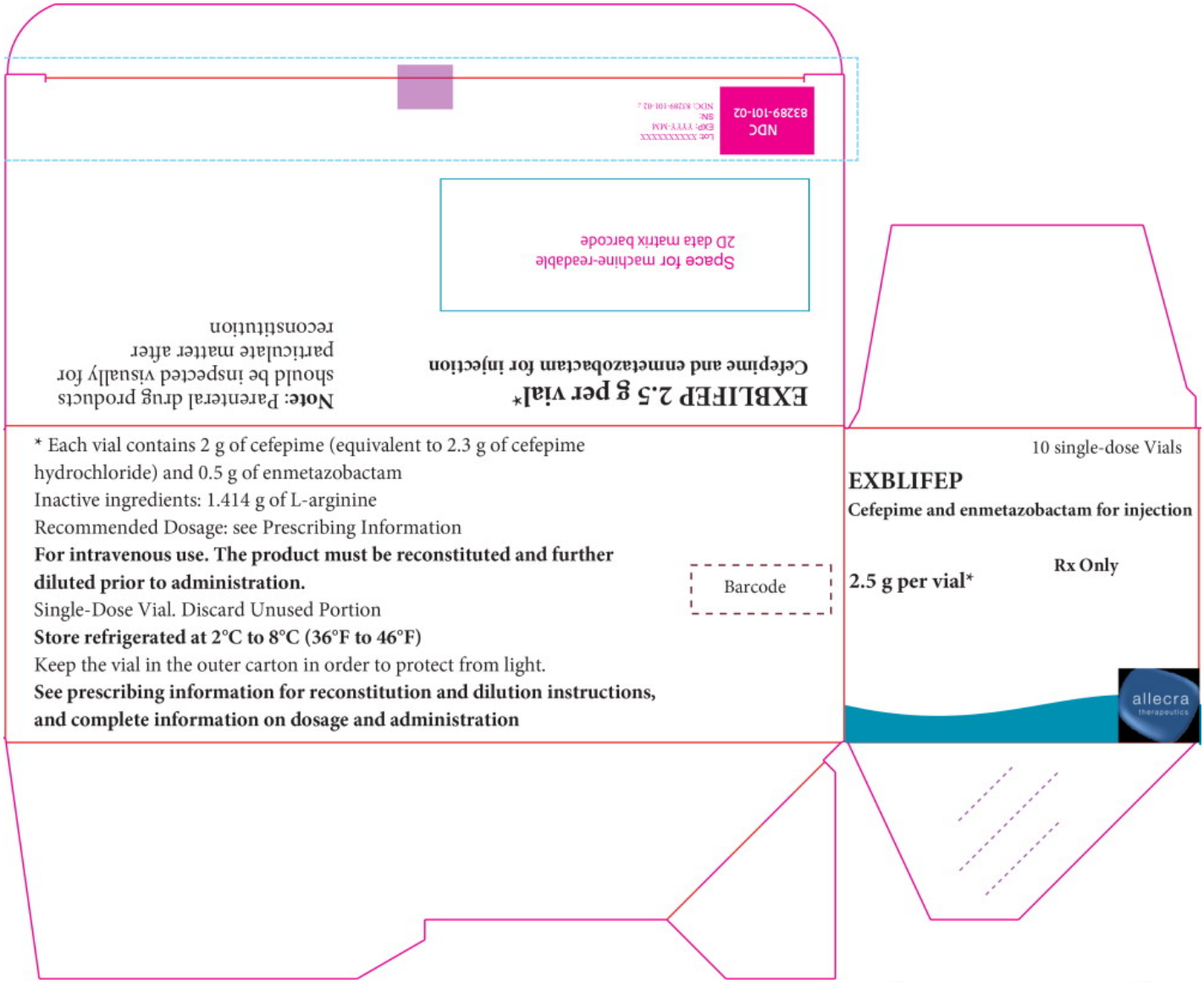
EXBLIFEP 2.5 g per vial *

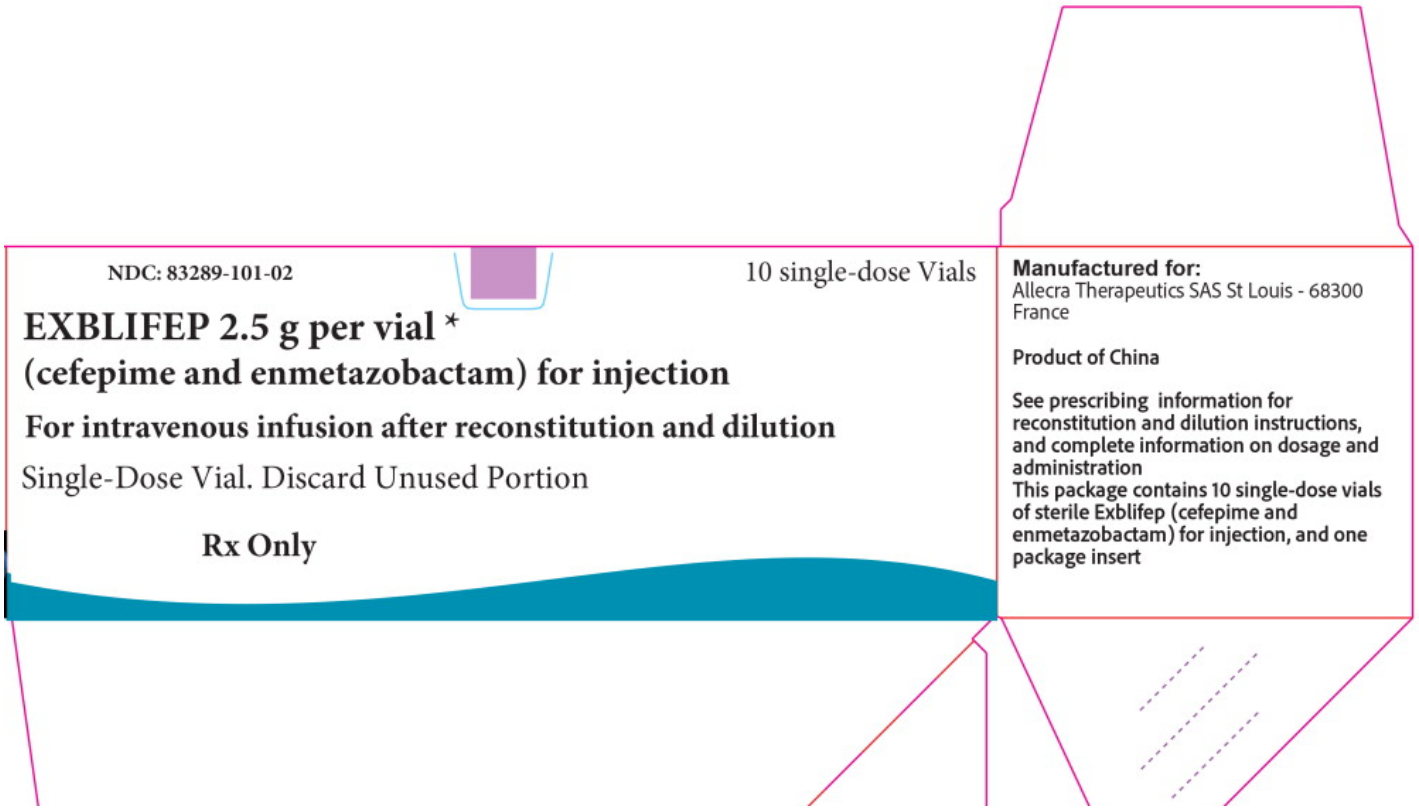
(cefepime and enmetazobactam) for injection

For intravenous infusion after reconstitution and dilution

Single-Dose Vial. Discard Unused Portion

Rx Only


NDC
83289-101-02
Space for machine-readable
2D data matrix barcode
EXBLIFEP 2.5 g per vial*
Cefepime and enmetazobactam for injection
Note: Parenteral drug products
should be inspected visually for
particulate matter after
reconstitution
* Each vial contains 2 g of cefepime (equivalent to 2.3 g of cefepime
hydrochloride) and 0.5 g of enmetazobactam
Inactive ingredients: 1.414 g of L-arginine
Recommended Dosage: see Prescribing Information
For intravenous use. The product must be reconstituted and further
diluted prior to administration.
Single-Dose Vial. Discard Unused Portion
Store refrigerated at 2°C to 8°C (36°F to 46°F)
Keep the vial in the outer carton in order to protect from light.
See prescribing information for reconstitution and dilution instructions,
and complete information on dosage and administration
Barcode
10 single-dose Vials
EXBLIFEP
Cefepime and enmetazobactam for injection
Rx Only
2.5 g per vial*
allecra
therapeutics


NDC: 83289-101-02
10 single-dose Vials
EXBLIFEP 2.5 g per vial *
(cefepime and enmetazobactam) for injection
For intravenous infusion after reconstitution and dilution
Single-Dose Vial. Discard Unused Portion
Rx Only
Manufactured for:
Allecra Therapeutics SAS St Louis - 68300
France
Product of China
See prescribing information for
reconstitution and dilution instructions,
and complete information on dosage and
administration
This package contains 10 single-dose vials
of sterile Exblifep (cefepime and
enmetazobactam) for injection, and one
package insert

EXBLIFEP

cefepime hydrochloride, enmetazobactam injection, powder, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:83289-101
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
cefepime hydrochloride (UNII: I8X1O0607P) (cefepime - UNII:807PW4VQE3)	cefepime	2 g
enmetazobactam (UNII: 80VUN7L00C) (enmetazobactam - UNII:80VUN7L00C)	enmetazobactam	0.5 g

Inactive Ingredients	
Ingredient Name	**Strength**
arginine (UNII: 94ZLA3W45F)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:83289-101-02	10 in 1 CARTON	02/28/2024	
1		1 in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA216165	02/28/2024	

Labeler - Allecra Therapeutics SAS (263514560)

Revised: 2/2024 Allecra Therapeutics SAS