TOTACEF-1000

(Cefepime for Injection USP 1000 mg)

1. NAME OF MEDICINAL PRODUCT

TOTACEF-1000 (Cefepime for Injection USP 1000 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TOTACEF-1000: Each vial contains Cefepime hydrochloride (sterile) USP equivalent to Cefepime 1000 mg (as a sterile mixture of Cefepime hydrochloride & L-Arginine)

L-arginine is used for pH adjustment

Excipients: For a full list of excipients, refer Section 6.1.

3. PHARMACEUTICAL FORMS

TOTACEF-1000: White to pale yellow powder. After reconstitution with sterilized water for injection it forms colourless to pale yellow colour solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pneumonia

Cefepime for Injection is indicated in the treatment of pneumonia (moderate to severe) caused by susceptible strains of *Streptococcus pneumoniae*, including cases associated with concurrent bacteremia, *Pseudomonas aeruginosa, Klebsiella pneumoniae,* or *Enterobacter species.*

Empiric Therapy for Febrile Neutropenic Patients

Cefepime for Injection as monotherapy is indicated for empiric treatment of febrile neutropenic patients. In patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia), antimicrobial monotherapy may not be appropriate.

Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis)

Cefepime for Injection is indicated in the treatment of uncomplicated and complicated urinary tract infections (including pyelonephritis) caused by susceptible isolates of *Escherichia coli* or *Klebsiella pneumoniae*, when the infection is severe, or caused by *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*, when the infection is mild to moderate, including cases associated with concurrent bacteremia with these bacteria.

Uncomplicated Skin and Skin Structure Infections

Cefepime for Injection is indicated in the treatment of uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes*.

Complicated Intra-abdominal Infections (used in combination with metronidazole)

Cefepime for Injection is indicated in the treatment of complicated intra-abdominal infections (used in combination with metronidazole) in adults caused by susceptible isolates of *Escherichia coli*, viridans group *streptococci*, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter species,* or *Bacteroides fragilis*

4.2 Dosage and Administration

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefepime for Injection and other antibacterial drugs, it should be used only to treat 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.

Adults

The recommended adult dosages and routes of administration are outlined in Table 1 below for patients with creatinine clearance greater than 60 mL/min. Administer Cefepime for Injection intravenously over approximately 30 minutes.

Table 1: Recommended Dosage Schedule for Cefepime for Injection in Adult Patients with Creatinine Clearance (CrCL) Greater Than 60 mL/min

Site and Type of Infection	Dose	Frequency	Duration (days)
Adults	Intravenous (IV)/Intramuscular (IM)		
Moderate to Severe Pneumonia[§]	1 to 2 g IV	Every 8 to 12 hours	10
Empiric therapy for febrile neutropenic patients	2 g IV	Every 8 hours	7*
Mild to Moderate Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis	0.5 to 1 g IV/IM**	Every 12 hours	7 to 10
Severe Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis	2 g IV	Every 12 hours	10
Moderate to Severe Uncomplicated Skin and Skin Structure Infections	2 g IV	Every 12 hours	10
Complicated Intra-abdominal Infections[§] (used in combination with metronidazole)	2 g IV	Every 12 hours	10

*or until resolution of neutropenia. In patients whose fever resolves but who remain neutropenic for more than 7 days, the need for continued antimicrobial therapy should be re-evaluated frequently. **Intramuscular route of administration is indicated only for mild to moderate, uncomplicated or complicated UTIs due to *E. coli*.

[§]For *P. aeruginosa*, use 2 g IV every 8 hours.

Pediatric Patients (2 months up to 16 years)

The maximum dose for pediatric patients should not exceed the recommended adult dose.

The usual recommended dosage in pediatric patients up to 40 kg in weight for durations as given above for adults is:

- 50 mg per kg per dose, administered every 12 hours for uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, and pneumonia (see below).
- For moderate to severe pneumonia due to P. aeruginosa give 50 mg per kg per dose, every 8 hours.
- 50 mg per kg per dose, every 8 hours for febrile neutropenic patients.

Dosage Adjustments in Patients with Renal Impairment

Adult Patients

Adjust the dose of Cefepime for Injectionin patients with creatinine clearance less than or equal to 60 mL/min to compensate for the slower rate of renal elimination. In these patients, the recommended initial dose of Cefepime for Injectionshould be the same as in patients with CrCL greater than 60 mL/min except in patients undergoing hemodialysis. The recommended doses of Cefepime for Injectionin patients with renal impairment are presented in Table 2.

When only serum creatinine is available, the following formula (Cockcroft and Gault equation) may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

$$\text{Males: Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: 0.85 × above value

Table 2: Recommended Dosing Schedule for Cefepime for Injection in Adult Patients with Creatinine Clearance Less Than or Equal to 60 mL/min

Creatinine Clearance (mL/min)	**Recommended Maintenance Schedule**			
Greater than 60	500 mg every 12 hours	1 g every 12 hours	2 g every 12 hours	2 g every 8 hours
30 to 60	500 mg every 24 hours	1 g every 24 hours	2 g every 24 hours	2 g every 12 hours
11 to 29	500 mg every 24 hours	500 mg every 24 hours	1 g every 24 hours	2 g every 24 hours
Less than 11	250 mg every 24 hours	250 mg every 24 hours	500 mg every 24 hours	1 g every 24 hours
Continuous Ambulatory Peritoneal Dialysis (CAPD)	500 mg every 48 hours	1 g every 48 hours	2 g every 48 hours	2 g every 48 hours
Hemodialysis*	1 g on day 1, then 500 mg every 24 hours there after			1 g every 24 hours

*On hemodialysis days, cefepime should be administered following hemodialysis. Whenever possible, cefepime should be administered at the same time each day.

In patients undergoing Continuous Ambulatory Peritoneal Dialysis (CAPD), Cefepime for Injection may be administered at the recommended doses at a dosage interval of every 48 hours (see Table 2).

In patients undergoing hemodialysis, approximately 68% of the total amount of cefepime present in the body at the start of dialysis will be removed during a 3-hour dialysis period. The dosage of Cefepime for Injection for hemodialysis patients is 1 g on Day 1 followed by 500 mg every 24 hours for the treatment of all infections except febrile neutropenia, which is 1 g every 24 hours.

Cefepime for Injection should be administered at the same time each day and following the completion of hemodialysis on hemodialysis days (see Table 2).

Pediatric Patients

Data in pediatric patients with impaired renal function are not available; however, since cefepime pharmacokinetics are similar in adults and pediatric patients, changes in the dosing regimen proportional to those in adults (see Tables 1 and 2) are recommended for pediatric patients.

Mode of Administration: For Intramuscular/Intravenous Use.

The reconstituted solution should be used immediately after preparation.

Do not use if the reconstituted solution is not clear or has suspended matter.

Constitute vials of Cefepime for Injection with sterile water for injection. Refer Table 3 for preparation of the constituted solutions of Cefepime for Injection

Table 3: Preparation of constituted solutions of Cefepime for Injection

Single-dose vials for intravenous (IV)/ Intramuscular (IM) administration	Amount of diluent to be added (ml)	Approximate available volume (ml)	Approximate Cefepime concentration (mg/ml)
Cefepime vial content			
1g (IV)	10	11.3	100
1g (IM)	2.4	3.6	280

As with other cephalosporins, the color of Cefepime for Injection, as well as its solutions tend to darken depending on storage conditions; however, when stored as recommended, the product potency is not adversely affected.

4.3 Contraindications

Cefepime for Injection is contraindicated in patients who have shown immediate hypersensitivity reactions to cefepime or the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.

4.4 Special Warning and Precautions for use

Hypersensitivity Reactions

Before therapy with Cefepime for Injection is instituted, careful inquiry should be made to determine whether the patient has had previous immediate hypersensitivity reactions to cefepime, cephalosporins, penicillins, or other beta-lactams. Exercise caution if this product is to be given to penicillin-sensitive patients because cross-hypersensitivity among beta-lactam antibacterial drugs has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Cefepime for Injection occurs, discontinue the drug and institute appropriate supportive measures.

Neurotoxicity

Serious adverse reactions have been reported 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 epileptic. 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 cefepime therapy occurs, discontinue cefepime and institute appropriate supportive measures.

Clostridium difficile Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Cefepime for Injection, 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 strains 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, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Development of Drug-Resistant Bacteria

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

As with other antimicrobials, prolonged use of Cefepime for Injection may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.

4.5 Interactions with other medicinal products and other form of interaction

Drug/Laboratory Test Interactions

Urinary Glucose

The administration of cefepime may result in a false-positive reaction for glucose in the urine when using some methods.

Coombs' Tests

Positive direct Coombs' tests have been reported during treatment with Cefepime For Injection. 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 antibiotics before parturition.

Prothrombin Time

Many cephalosporins, including cefepime, have been associated with a fall in prothrombin activity. Those at risk 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.

Aminoglycosides

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

Diuretics

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

4.6 Pregnancy and Lactation

Pregnancy

Pregnancy category B. There are no adequate and well-controlled studies of cefepime use in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Cefepime is excreted in human breast milk. Caution should be exercised when cefepime is administered to a nursing woman.

Use in special population:

Pediatric use:

The safety and effectiveness of cefepime in the treatment of uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, pneumonia, and as empiric therapy for febrile neutropenic patients have been established in the age groups 2 months up to 16 years. Safety and effectiveness in pediatric patients below the age of 2 months have not been established

Geriatric Use:

This drug is known to be substantially excreted by the kidney, and the risk of toxic 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.

Renal Impairment:

Adjust the dose of Cefepime in patients with creatinine clearance less than or equal to 60 mL/min to compensate for the slower rate of renal elimination

4.7 Undesirable Effects

The following adverse reactions are discussed in the Section 4.4,Special Warnings and Precautions section:

- Hypersensitivity Reactions
- Neurotoxicity
- *Clostridium difficile*-Associated Diarrhea

In addition to the adverse reactions listed above that have been observed in patients treated with cefepime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibacterial; drugs

Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic dysfunction including cholestasis, and pancytopenia.

4.8 Overdose

Patients who receive an overdose should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis, not peritoneal dialysis, is recommended to aid in the removal of cefepime from the body. Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, neuromuscular excitability and nonconvulsive status epilepticus.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Antibacterial for systemic use, cephalosporins, ATC Code: J01DE01

Cefepime is a cephalosporin antibacterial drug.

Mechanism of action

Cefepime is a bactericidal drug that acts by inhibition of bacterial cell wall synthesis. Cefepime has a broad spectrum of in vitro activity that encompasses a wide range of Gram-positive and Gram-negative bacteria. Within bacterial cells, the molecular targets of cefepime are the penicillin binding proteins (PBP).

Antimicrobial activity

Cefepime has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections as described in the Therapeutic Indications (Section 4.1).

Gram-negative Bacteria: *Enterobacter spp., Escherichia coli ,Klebsiella pneumoniae, Proteus mirabilis,Pseudomonas aeruginosa*

Gram-positive Bacteria: *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus pneumonia, Streptococcus pyogenes,* Viridans group streptococci

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 cefepime against isolates of similar genus or organism group. However, the efficacy of cefepime in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive Bacteria: *Staphylococcus epidermidis* (methicillin-susceptible isolates only), *Staphylococcus saprophyticus, Streptococcus agalactiae*

NOTE: Most isolates of enterococci, e.g., *Enterococcus faecalis*, and methicillin-resistant staphylococci are resistant to cefepime.

Gram-negative Bacteria: *Acinetobacter calcoaceticus subsp. Lwoffii, Citrobacter diversus, Citrobacter freundii, Enterobacter agglomerans , Haemophilus influenza, Hafnia alvei*, *Klebsiella oxytoca, Moraxella catarrhalis, Morganella morganii , Proteus vulgaris, Providencia rettgeri , Providencia stuartii , Serratia marcescens*

NOTE: Cefepime is inactive against many isolates of *Stenotrophomonas maltophilia.*

5.2 Pharmacokinetics Properties

Absorption: Following intramuscular (IM) administration, cefepime is completely absorbed.

Distribution: The average steady-state volume of distribution of cefepime is 18 (±2) L. The serum protein binding of cefepime is approximately 20% and is independent of its concentration in serum.

Cefepime is excreted in human milk at a concentration of 0.5 mcg/mL. A nursing infant consuming approximately 1000 mL of human milk per day would receive approximately 0.5 mg of cefepime per day.

Metabolism and Excretion

Cefepime is metabolized to N-methylpyrrolidine (NMP) which is rapidly converted to the N-oxide (NMP-N-oxide). Urinary recovery of unchanged cefepime accounts for approximately 85% of the administered dose. Less than 1% of the administered dose is recovered from urine as NMP, 6.8% as NMP-N-oxide, and 2.5% as an epimer of cefepime. Because renal excretion is a significant pathway of elimination, patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment.

Patients with Renal impairment

Cefepime total body clearance decreased proportionally with creatinine clearance in patients with abnormal renal function, which serves as the basis for dosage adjustment recommendations in this group of patients.

Patients with Hepatic impairment

The pharmacokinetics of cefepime were unaltered in patients with hepatic impairment

Geriatric patients

Dosage administration of cefepime in the elderly should be adjusted as appropriate if the patient's creatinine clearance is 60 mL/min or less.

5.3 Pre-Clinical Safety Data

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. 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 body surface area basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

None

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Dry Powder: 24 months from the date of manufacture.

Reconstituted product: Refer section 6.4

6.4 Special Precautions for Storage

Storage prior to reconstitution: Store below 30° C. Protect from light.

The reconstituted solution should be used immediately after preparation.

Storage after reconstitution: Store the reconstituted solution for not more than 24 hours at 2-8°C. Do not freeze.

Discard any unused solution.

Keep out of the reach and sight of children.

6.5 Nature and Contents of Container

20 ml clear transparent glass vial USP Type-I with bromobutylated rubber stopper & aluminium flip off seal caps, containing sterile white to pale yellow powder. One such vial is packed in a unit carton along with a package insert.

6.6 Special Precautions for Disposal

No special requirements.

7. DATE OF PUBLICATION OF INSERT

June' 2021

Manufactured by:
MANKIND PHARMA LTD.
Village - Kishanpura, P.O. Jamni wala, Tehsil-Paonta Sahib,
Distt. Sirmour-173025, Himachal Pradesh, (INDIA)

Regd. Office: 208, Okhla Industrial Estate,
Phase-3, New Delhi-110 020 (INDIA)