SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Deltacef 500 mg powder for solution for injection or infusion
Deltacef 1 g powder for solution for injection or infusion
Deltacef 2 g powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 0.5g, 1g or 2g cefepime (as cefepime dihydrochloride monohydrate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.
White to pale yellow powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults
Deltacef is used to treat the infections caused by cefepime-susceptible pathogens:

- Lower respiratory tract infections (pneumonia, bronchitis)
- Urinary tract infections (uncomplicated and complicated urinary tract infections, including pyelonephritis)
- Skin and soft-tissue infections
- Intra-abdominal infections (peritonitis, biliary tract infections)
- Gynecological infections
- Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above
- Empirical treatment of patients with febrile neutropenia
  Cefepime as monotherapy is indicated as empirical treatment in patients with febrile neutropenia. In patients at high risk of severe infections (e.g. patients with recent bone marrow transplantation, patients with hypotension, patients with an underlying hematological malignancy or patients with severe or prolonged neutropenia), antimicrobial monotherapy may be inappropriate. There are

insufficient data to support the efficacy of cefepime monotherapy in such patients (see section 5.1).
- Prophylactic antimicrobial therapy for patients undergoing surgical procedures (see section 5.1).

Paediatric population Deltacef is indicated in children older than 2 months for the treatment of infections caused by cefepime-susceptible pathogens:
- Pneumonia
- Skin and soft tissue infections
- Urinary tract infection (uncomplicated and complicated urinary tract infections, including pyelonephritis)
- Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above
- Cefepime as monotherapy is indicated as empirical treatment in patients with febrile neutropenia. In patients at high risk of severe infections (e.g. patients with recent bone marrow transplantation, patients with hypotension, patients with an underlying hematological malignancy or patients with severe or prolonged neutropenia), antimicrobial monotherapy may be inappropriate. There are insufficient data to support the efficacy of cefepime monotherapy in such patients (see section 5.1).
- Bacterial meningitis

In order to determine possible causes, culture and antibiogram should be done whenever possible. Empirical treatment with Deltacef can be started before the results of these tests were obtained, however, once obtained, antibiotic treatment should be adjusted accordingly. Because of its broad bactericidal activity against gram positive and gram negative microorganisms, Deltacef may be used as a single agent even prior identifying the infective agent and its sensitivity to cefepime (see section 5.1). In patients with a high risk of combined aerobic-anaerobic infection, especially if the microorganism is not sensitive to cefepime, it is recommended that the initial treatment start simultaneously with the anti-anaerobic drugs even prior identifying the infective agent. When results become available, combination treatment with Deltacef and with other antibiotics may not be necessary.

4.2. Dosage and administration

Dosage and route of administration vary depending on the type and severity of infection, renal function and general condition of the patient. Deltacef can be administrated intravenously or in a deep intramuscular injection. The preparation of solutions of Deltacef is summarized in Table 1.

Table 1 Preparation of solution of Deltacef

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)**
IV			
Vial content 0.5g	5	5.6	90
Vial content 1g	10	11.4	90
Vial content 2g	10	12.8	100
IM			
Vial content 0.5g	1.5	1.8	280
Vial content 1g	3	4.4	230

Intravenous administration:

Intravenous administration is to be preferred in patients with severe or life-threatening infections, particularly when the possibility of shock is present.

For direct intravenous injection of Deltacef, the solution is reconstituted as recommended in sterile water for injections, in 5% glucose for injection or in 0,9% normal saline solution according to Table1. Intravenous injection should be slowly injected directly into the vein over a period of three to five minutes. Alternatively, the injection can be made into the tubing of an administration set while the patient is receiving a compatible intravenous fluid (see section 6.2).

For continuous intravenous infusion, reconstitute the solution of Deltacef as recommended (same way as for direct intravenous injection) and add an appropriate quantity of the resulting solution to one of the compatible intravenous fluids (see section 6.2) in an intravenous administration set. The resulting solution should be administrated over a period of approximately 30 minutes.

Intramuscular administration:

Deltacef should be constituted with one of the following diluents according to Table1: Water for injection, 0,9% normal saline solution, 5% glucose for injection or Bacteriostatic Water for Injection (benzyl Alcohol or parabens) and is given by deep intramuscular injection into a large muscle mass(such as the upper outer quadrant of the gluteus maximus).

Although Deltacef can be constituted with 0.5% or 1.0% lidocaine hydrochloride, it is usually not required since cefepime causes little or no pain upon intramuscular administration.

Dosing recommendations:

Adult and adolescents over 40kg body weight

Dosing recommendations for adults and adolescents over 40 kg body weight with normal renal function are provided in the following Table 2:

Table 2 Recommended Dosage Schedule for adults and adolescents over 40 kg with normal renal function*

Severity of infection	**Dose and route of administration**	**Dosing interval**
Mild to moderate Urinary Tract Infections	0.5-1g IV or IM	12h
Mild to moderate infections other than Urinary Tract Infections	1g IV or IM	12h
Severe infections	2g IV	12h
Extremely severe or life-threatening infections	2g IV	8h

*Optimal duration of therapy is 7-10 days. Severe infections may require longer therapy. For febrile neutropenia, the duration of therapy should not be less than 7 days until neutropenia resolves.

For prophylaxis in intra-abdominal surgery (adults)

Single IV dose of 2g Deltacef is administrated as a 30 minute infusion 60 minutes before the procedure; thereafter, IV 500mg metronidazole should be given. The metronidazole dose should be reconstituted and administrated according to the official Summary of Product Characteristics. Due to incompatibility between Deltacef and metronidazole, these two active substances must not be administrated together (see section 6.2). Prior to infusing metronidazole, it is recommended that the infusion tube be flushed with a compatible fluid. If the procedure lasts for more than 12 hours, the dose of Deltacef should be repeated after 12 hours but never repeat the dose of metronidazole.

Patients with impaired renal function

In patients with impaired renal function the dose of cefepime must be adjusted in order to compensate its decreased renal excretion.

The recommended starting dose of cefepime for patients with mild to moderate impaired renal function is the same as for the patients with normal renal function. The maintenance dose for adults with renal dysfunction is provided in Table 3.

Table 3 Maintenance dose for adults with renal dysfunction

Creatinine	**Recommended maintenance dose**

	Extremely severe/life threatening infection	**Severe infection**	**Mild to moderate infections other than Urinary Tract Infections**	**Mild to moderate Urinary Tract Infections**
More than 50	Usual dose, no adjustment needed			
	2g/8 hourly	2g/12 hourly	1g/12 hourly	500 mg/12 hourly
30-50	2g/12 hourly	2g/daily	1g/daily	500mg/daily
11-29	2g/daily	1g/daily	500mg/daily	500mg/daily
≤10	1g/daily	500mg/daily	250mg/daily	250mg/daily
Hemodialysis*	500mg/daily	500mg/daily	500mg/daily	500mg/daily

*Pharmacokinetic models show the necessity to reduce the dose in those patients.

The dosing recommendation of cefepime in patients undergoing hemodialysis is the following:
First day of therapy: 1g
There after 500mg daily for all infections, except febrile neutropenia.
Febrile neutropenia: 1 g daily. When undergoing hemodialysis, cefepime should be given after the end of the procedure. If possible cefepime should be administrated at the same hour.
If only the serum creatinine level is available, creatinine clearance (CRCL ml/min) can be approximated using Cockcroft-and Gault equation.
The serum creatinine should represent a steady state of renal function:
American equation
Male patient: CRCL (ml/min) = weight (kg) x (140-age [in years])/72 x SCR (mg/dl)
European equation:
Male patient: CRCL (ml/min) = weight (kg) x (140-age [in years]) x 1.23/72 x SCR (mg/dl)
Female patient: CRCL (ml/min) = 0.85 x male value

Dialysis patients:
If hemodialysis is performed, approximately 68% of the total amount of cefepime at the start of dialysis will be removed during a 3 hour dialysis session.
In cases of continuous ambulatory peritoneal dialysis, Deltacef can be administrated at the usual doses recommended for patients with normal renal function, e.g. 500 mg, 1g or 2g accordingly to the severity of the infection, but at 48-hour intervals only.

Patients with impaired hepatic function:
No adjustment is needed in patients with impaired hepatic function.

Dosing recommendations in children with normal renal function

Pneumonia, UTIs, skin and soft-tissue infections:

Children older than 2 months and body weight less than 40kg: 50mg/kg per dose, given every 12 hours for 10 days. If severe infection, the dose should be given every 8 hr.

Sepsis, bacterial meningitis and empirical treatment of febrile neutropenia:

Children older than 2 months and body weight less than 40 kg: 50mg/kg per dose, given every 8hours for 7-10 days.

There is no official data on the use of Deltacef in children aged less than 2 month. However based on the model-based clinical pharmacokinetic dosing of 50 mg/kg per dose in children older than 2 months, the dose of 30 mg/kg every 12 or 8 hours could be considered in children aged between 1 and 2 months. Both doses of 50 mg/kg per dose in children older than 2 months and 30 mg/kg per dose in children aged between 1 and 2 months are comparable with doses of 2g in adults. Close monitoring is highly recommended.

The adult dosing recommendations are also valid for children with body weight over 40 kg. The pediatric dosage should not exceed the adult maximum dose of 2g every 8 hours.

Limited data for IM administration in children.

Children with impaired renal function:

As Deltacef is exclusively excreted via the kidneys, the dose should also be adjusted for patients with impaired renal function (See Table 3).

If only the serum creatinine level (SCR) is available, creatinine clearance (CRCL) can be determined using the following formula:

CRCL (ml/min/1.73 m^2) = 0.55 x height (cm)/SCR (mg/dl) or

CRCL (ml/min/1.73 m^2) = 0.52 x height (cm)/SCR (mg/dl)a-3.6

Elderly patients:

As the like hood of suffering from reduced renal function is greater in elderly patients, caution should be exercised when selecting the dose for these patients and renal function should be monitored.

4.3 Contraindications

Cefepime is contraindicated in patients who have had previous hypersensitivity reactions to cefepime, to any of the excipients listed in section 6.1, to any other cephalosporin or to any other beta-lactam antibiotics agent (e.g. penicillins, monobactams and carbapenems).

4.4. Special warnings and precautions for use

Hypersensitivity reactions

As with all beta-lactam antibacterial agents, severe and occasionally fatal hypersensitivity reactions have been reported.

Before therapy with cefepime is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefepime, beta-lactams or other medicinal products.

Cefepime should be administered with caution to patients with a history of asthma or allergic diathesis. The patient must be carefully monitored during the first administration. If an allergic reaction occurs, treatment must be discontinued immediately.

Serious hypersensitivity reactions may require epinephrine and other supportive therapy.

Antibacterial activity of cefepime

Due to the relatively limited spectrum of antibacterial activity of cefepime it is not suitable for treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a very high suspicion that the most likely pathogen(s) would be suitable for treatment with cefepime (see section 5.1).

Renal impairment

In patients with impaired renal function (creatinine clearance ≤ 50ml/min) or other conditions that can impair renal function, the dosage of cefepime should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dosage should be reduced when cefepime is administered to such patients. Continued dosage dosage should be determined by the degree of renal impairment, severity of infection and susceptibility of the causative organisms (see sections 4.2 and 5.2).

During post-marketing surveillance, the following serious adverse events have been reported: reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures (including non-convulsive status epilepticus), and/or renal failure (see section 4.8). Most cases occurred in patients with renal impairment who received doses of cefepime that exceeded recommendations.

In general, symptoms of neurotoxicity resolved after discontinuation of cefepime and/or after haemodialysis, however, some cases included a fatal outcome.

Clostridium difficile associated diarrhoea

Clostridium difficile–associated diarrhoea (CDAD) has been observed with the use of nearly all broad-spectrum antibacterial agents, including cefepime, and varies in severity from mild diarrhoea to life-threatening pseudomembranous colitis. CDAD must be considered in all patients with diarrhoea following antibiotic use. A precise medical history is needed, as cases of CDAD have been reported for up to 2 months after administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic treatment not targeted against C. difficile must be discontinued immediately.

Interference with serological testing

A positive Coombs test, without evidence of haemolysis, has been described in patients treated with cefepime twice daily.

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

Elderly patients:

Out of more than 6,400 adults treated with cefepime as part of clinical studies, 35% were over 65 years of age, whilst 16% were over 75 years. In clinical studies, safety and efficacy in geriatric patients given the normal adult dose were comparable with non-geriatric patients, provided that these patients were free from any renal dysfunction. Compared with younger patients, there was merely a slight prolongation in the elimination half-life and lower renal clearance. The dose should be adjusted in cases of renal dysfunction (see section 4.2). As cefepime is mainly excreted via the kidneys, the risk of toxic effects is greater in patients with renal dysfunction. As the like hood of suffering from reduced renal function is greater in elderly patients, caution should be exercised when selecting the dose for these patients and renal function should be monitored (see section 4.8 and 5.1.). Severe adverse reactions occurred in elderly patients with renal impairment whose cefepime dose was not adjusted, including reversible encephalopathy (impaired consciousness with confusion, hallucinations, stupor and coma), myoclonus, seizures (including non-convulsive status epilepticus) and /or renal failure (see section 4.8).

4.5. Interaction with other medicinal products and other forms of interaction

No available study.
Concomitant treatment with bacteriostatic antibiotics may interfere with the action of beta lactam antibiotics.
There is a risk of bleeding in combination with anticoagulants, antiplatelet and antiagregant therapy.
Probenecid slows renal elimination of cefepime and then amplifies its action.
Cefepime causes disulfiram (antabus) reaction in combination with alcohol drinks with nausea and vomiting.
Non-enzymatic methods for determining urinary glucose may also give a false-positive result.

4.6. Fertility, pregnancy and lactation

Pregnancy
The safety of using cefepime in pregnant women has not been substantiated.
Studies evaluating mice and rabbit models showed no direct or indirect impact on foetus. However there are insufficient data to evaluate the impact of cefepime on fertility, foetus evolution, delivery and postnatal evolution (see section 5.3).
Potential risk for human is unknown. During pregnancy, cefepime should only be used when the anticipated benefit justifies the potential risk.

Breastfeeding
Very small concentrations of cefepime are excreted in breast milk. Deltacef should only be used, with precautions, when the anticipated benefit justifies the potential risk.

Fertility
No impairment of fertility has been seen in rats. There are no data on the use of cefepime in human fertility.

4.7. Effects on ability to drive and use machines

The effects of medicinal product on ability to drive and use machines have not been studied. However, possible adverse reactions like altered state of consciousness, dizziness, confusional state or hallucinations may alter the ability to drive and use machines (see sections 4.4, 4.8).

4.8. Undesirable effects

In patients treated with cephalosporin-class antibiotics the following adverse reactions and altered laboratory tests have been reported: Stevens-Johnson syndrome, erythema multiforme, toxic

epidermal necrolysis, toxic neuropathy, aplastic anaemia, haemolytic anaemia, bleeding and urinary glucose false-positive result.

Cefepime is generally well tolerated, the most common adverse reactions observed in clinical studies (N=5598) are GIT disturbances and hypersensitivity reaction. The adverse reactions are listed as common, likely and possible.

Adverse reactions with incidence >0.1-1%:
Hypersensitivity: rash (1.8%), pruritus, urticarial
GIT symptoms: nausea, vomiting, oral moniliasis, diarrhoea (1.2%), colitis (including pseudomembranous colitis).
CNS: headache.
Other reactions: fever, vaginitis, erythema.

Adverse reactions with incidence <0.05-0.1%:
Abdominal pain, constipation, vasodilatation, dyspnea, dizziness, paresthesia, genital pruritus, change of taste, tremor, non-specific candidiasis.

Adverse reactions with incidence <0.05%:
Anaphylactic reactions, convulsions

Common reactions at the site of infusion found in 5.2% of patients:
Phlebitis (2.9%) and inflammation.
Intramuscular administration is very well tolerated, only 2.6% of patients present pain and inflammation at the site of injection.

Postmarketing experience
The following adverse experiences have been reported during worldwide postmarketing experience.
Undesirable effects are classified into the Table 4, according to system organ class and incident frequency: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1/10,000) and not known (frequency cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4 Undesirable effects reported in clinical studies or during postmarketing experience (MedDRA term)

System organ class	Frequency	MedDRA term
Infections and infestations	Uncommon	Oral candidiasis, vaginal infection
	Rare	Candidiasis
Blood and lymphatic system disorders	Very common	Positive Coombs' test
	Common	Rise in prothrombin and partial thromboplastin time, anemia, eosinophilia
	Not known	Aplastic anemia, haemolytic anemia, agranulocytosis
Immune system disorders	Rare	Anaphylactic reaction, Angioedema
	Not known	Anaphylactic shock
Metabolism and nutrition disorders	Not known	False-positive results for urinary glucose tests
Psychiatric disorders	Not known	Confusion, hallucinations
Nervous system disorders	Uncommon	Headache
	Rare	Seizures, paraesthesia, dysgeusia, dizziness
	Not known	Coma, stupor, encephalopathy, impaired consciousness, myoclonus
Vascular disorders	Common	Phlebitis at the injection site
	Rare	Vasodilatation
	Not known	Haemorrhage
Respiratory, thoracic and mediastinal disorders	Rare	Dyspnea
Gastrointestinal disorder	Common	Diarrhoea
	Uncommon	Pseudomembranous colitis, colitis, nausea, vomiting
	Rare	Abdominal pain, constipation
	Not known	Gastrointestinal complains
Hepatobiliary disorders	Common	Increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin

System organ class	Frequency	MedDRA term
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Erythema, urticaria, pruritus
	Not known	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
Renal and urinary tract disorders	Uncommon	Increase in BUN and serum creatinine
	Not known	Renal failure, toxic nephropathy
Reproductive system and breast disorders	Rare	Genital pruritus
General disorders and administration site conditions	Common	Reactions at the site of infusion, pain and inflammation at the site of injection
	Uncommon	Fever
	Rare	Shivering
Investigations	Common	Increase in alkaline phosphatase

a: This adverse reactions are generally accepted to be a class side effects.

Paediatric population: In babies, infants and children, the safety profile of cefepime was similar to that of adults. In clinical studies, rash was the most commonly occurring adverse reaction to have any causal relationship with cefepime.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit / risk balance of the medicinal product. Any suspected adverse reactions should be reported to Pharmaceutical Services, Ministry of Health, CY-1475, www.moh.gov.cy / phs Fax: + 357 22608649.

4.9. Overdose

In cases of severe overdose, particularly in patients with impaired renal function, hemodialysis can assist in elimination cefepime from the body. Peritoneal dialysis has no benefit. Unintentional overdose has occurred when patients with renal dysfunction were administrated high doses (see sections 4.2 and 4.3). Symptoms of an overdose include encephalopathy (impaired consciousness

including confusion, hallucinations, stupor and coma), myoclonic seizures and neuromuscular excitability (see section 4.8).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: 4th generation cephalosporin, ATC code: J01DE01

Cefepime is a broad spectrum 4th generation cephalosporin for intravenous and intramuscular use.
Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. . Cefepime has a broad spectrum antibacterial, that acts both to gram-positive and gram-negative bacteria, inclusive most of strains resistant to aminoglycosides and to 3rd generation of cephalosporins. Cefepime is highly resistant to hydrolysis by most beta-lactamases and exhibits rapid penetration into gram – negative bacterial cells. Cefepime has a low affinity for chromosomally-encoded beta-lactamases.

Clinical trials showed that with within bacterial cells (Escherichia Coli and Enterobacter cloacae), the molecular targets of cefepime are the penicillin binding proteins (PBP) 3, sometimes (PBP) 2 and PBP 1a and 1b. The affinity of cefepime to PBP 2 following parenteral administration is important compared to the affinity to other parenteral cephalosporins which increases its antibacterial activity. Mild affinity of cefepime to PBP 1a and 1b is also noted which also increases its antibacterial activity.
Cefepime is a bactericidal agent that acts against most strains by using the method “Time Kill Assay” by determining the minimum bactericidal inhibitory concentration (MBC).
Minimum inhibitory and bactericidal concentrations (MIC and MBC, respectively)-MBC/MIC ratios were ≤ 2 for cefepime in 80% of tested isolated gram-positive and gram-negative bacterial strains. Synergy with aminoglycosides was noted in vivo activity mainly against isolated bacterial strains of Pseudomonas aeruginosa.

Cefepime has been shown to be active against most strains of the following microorganisms:

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus (methicillin-susceptible strains only)
Staphylococcus epidermidis (including beta-lactamase producing strains)
Staphylococcus hominis
Staphylococcus saprophyticus
Staphylococcus pyogenes (including group A streptococci)
Staphylococcus agalactiae (Streptococcus group B)

Staphylococcus pneumoniae (including strains with mild resistance against penicillin with MIC 0.1-1 µg/ml)
Other beta-hemolytic streptococci (group C, G, F)
Streptococcus bovis (group D)
Streptococcus viridians

Aerobic Gram-Negative Microorganisms:
Acinetobacter calcoaceticus (sp. anitratus, lwoffi)
Aeromonas hydrophilla
Capnocytophaga sp.
Citrobacter sp. (including C. diversus, C. freundii)
Campylobacter jejuni
Enterobacter sp. (including E. cloacae, E. aerogenes, E. sakazakii)
Escherechia coli
Gardnerella vaginalis
Haemophilus ducreyi
Haemophilus influenzae (including beta-lactamase producing strains)
Haemophilus parainfluenzae
Hafnia alvei
Klebsiella sp. (including K. pneumoniae, K. oxytoca, K. ozaenae)
Legionella sp.
Morganella morganii
Moraxella catarrhalis (Branhamella catarrhalis, including beta-lactamase producing strains)
Neisseria meningitides
Pantoea agglomerans (formerly Enterobacter agglomerans)
Proteus sp. (including P. mirabilis, P. vulgaris)
Providencia sp. (including P. rettgeri, P. stuartii)
Pseudomonas sp. (including P.aeruginosa, P. putida, P. stutzeri)
Salmonella sp.
Serratia (including S.marcescens, S. liquefaciens)
Shigella sp.
Yersinia enterocolitica

NOTE: Cefepime is inactive against most strains of Stenotrophomonas (formerly Xanthomonas maltophilia [Pseudomonas maltophilia]).

Anaerobic Microorganisms:

Bacteroides sp.
Clostridium perfringers
Fusobacterium sp.
Mobiluncus sp.
Peptostreptococcus sp.
Pervotella melaninogenica (formerly Bacteroides melaninogenicus)
Veillonella sp.

NOTE: Cefepime is inactive against most strains of Clostridium fragilis and Clostridium difficile.

The prevalence of resistance in individualized bacterial strains may vary according to the region and time, so it is recommended to obtain local information about the susceptibility of the strains before initiating the treatment.

CLINICAL STUDIES

Febrile Neutropenic Patients

The safety and efficacy of empiric cefepime monotherapy of febrile neutropenic patients have been assessed in two multicentre, randomized trails, comparing cefepime monotherapy (at a dose of 2g IV q 8h) to ceftazidime monotherapy (at a dose of 2 g IV q 8 h). These studies comprised 317 evaluable patients.

Table 5 Pooled Response for Empiric Therapy of febrile Neutropenic Patients

Outcome measures	**% Response**	
	Cefepime (n=164)	**Ceftazidime (n=153)**
Primary episode resolved with no treatment modification, no new febrile episodes or infection, and oral antibiotics allowed for completion of treatment	51	55
Primary episode resolved with no treatment modification, no new febrile episodes or infection, and no post-treatment oral antibiotics	34	39
Survival, any treatment modification allowed	93	97
Primary episode resolved with no treatment modification and oral antibiotics allowed for completion of treatment	62	67
Primary episode resolved with no treatment modification and no post-treatment oral antibiotics	46	51

Insufficient data exist to support the efficacy of cefepime monotherapy 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). No data are available in patients with septic shock.

Patients older than 19 years (age average 66 years) who undergone colorectal surgery participated in a randomized, double-blind, multicentre trial comparing, post-surgery administration, the combination of 2g intravenous dose of cefepime plus 500 mg intravenous dose of metronidazole(n=307) versus 2 g intravenous dose of ceftriaxone plus metronidazole (n=308). The dose was given 0-3 hours prior surgery. The overall clinical cure rate (no local infection and no intra-abdominal infection during 6 weeks after surgery) among the both protocol-valid patients was 75% (see section 4.2)

The following reversible adverse laboratory changes related to therapy with cefepime were seen during conducted clinical trials in patients with normal baseline values:

Incidence between 1% and 2%:

Increased ALT (3.6%)

Increase AST (2.5%)

Increased alkaline phosphatase

Increased total bilirubin

Anemia, eosinophilia

Prolonged prothrombin time and prolonged partial thromboplastin time (2.8%)

Positive Coombs' without hemolysis (18.7%)

Transient increased in BUN and/or creatinine in serum and transient thrombocytopenia were seen in 0.5%-1% of patients

Transient leukopenia and neutropenia were seen in less than 0.5% of patients.

5.2. Pharmacokinetic properties

Adults

The average plasma concentrations of cefepime observed in healthy adult male following single 30-minutes infusions (IV) or intramuscular (IM) administration of cefepime 500 mg, 1g and 2g are summarized in Table 6.

Table 6 Average Plasma Concentrations in mg/ml of Cefepime in healthy, adult males

Parameter	500 mg IV	1g IV	2g IV	500 mg IM	1g IM	2g IM
0.5h	38.2	78.7	163.1	8.2	14.8	36.1

1.0h	21.6	44.5	85.8	12.5	25.9	49.9
2.0h	11.6	24.3	44.8	12	26.3	51.3
4.0h	5	10.5	19.2	6.9	16	31.5
8.0h	1.4	2.4	3.9	1.9	4.5	8.7
12.0h	0.2	0.6	1.1	0.7	1.4	2.3

Following intramuscular (IM) administration, cefepime is completely absorbed.
Concentrations of cefepime achieved in specific tissues and body fluids are listed in Table7.

Table 7 Average concentrations of cefepime in specific Body Fluids (µg/ml) or Tissues (µg/g)

Tissue or Fluid	**Dose/route**	**Average Time of Sample Post-Dose(h)**	**Average concentration**
Urine	500mg IV	0-4	292 µg/ml
	1gIV	0-4	926 µg/ml
	2gIV	0-4	3120 µg/ml
Bile	2gIV	9.4	17.8 µg/ml
Peritoneal Fluid	2gIV	4.4	18.3 µg/ml
Blister fluid	2gIV	1.5	81.4 µg/ml
Bronchial mucosa	2gIV	4.8	24.1 µg/ml
Sputum	2gIV	4	7.4 µg/ml
Prostate	2gIV	1	31.5 µg/ml
Appendix	2gIV	5.7	5.2 µg/ml
Gallbladder	2gIV	8.9	11.9 µg/ml

Cefepime is metabolised to N-methylpyrrolidine which is rapidly converted to the N-oxide. Approximately 85% of the administrated dose of cefepime is excreted by urine. Less than 1% of the administrated dose is recovered from urine as N-methylpyrrolidine, 6.8% as N-oxide and 2.5% as an epimer of cefepime. The average protein binding ratio is 16.4% and is not related to the plasma concentration.
Elimination of cefepime is principally via renal excretion with an average half-life of 2.0 hours, total body clearance of 120.0 ml/min and average renal clearance of 10.0 ml/min. Cefepime has linear pharmacokinetics over the range 250 mg to 2 g. There is no evidence of accumulation in healthy volunteers receiving clinically relevant doses for a period of 9 days.

Special Populations

Cefepime has been investigated in patients with acute pulmonary exacerbation of cystic fibrosis (n=24, age average 15 years, age range 5-47 years). Bacterial eradication is not reached in this group of patients treated with cefepime. No relevant clinical changes in cefepime pharmacokinetics were noted in patients with cystic fibrosis.

Impaired renal function

In patients with impaired renal function, there is a linear relationship between total body clearance and creatinine clearance which serves as the basis for dosage adjustment recommendations in this group of patients (see section 4.2). The average half-life of cefepime in patients requiring haemodialysis was 13 hours and in patients requiring continuous peritoneal dialysis was 19 hours.

Hepatic Insufficiency

The pharmacokinetics of cefepime were unaltered in patients with impaired hepatic function who received a single 1g dose. No dose adjustment is required in this group of patients.

Geriatric patients

Cefepime pharmacokinetics in single dose of 1g IV have been investigated in elderly health volunteers, 65 years of age and older, in whom slight prolongation of the elimination half-life and lower renal clearance values were observed. Dose adjustment is required when there is concomitant impairment of renal function (see section 4.2).

Paediatric patients

Cefepime pharmacokinetics have been evaluated in paediatric patients from 2.1 months to 11.2 years of age following single IV/IM dose of 50mg/kg and multiple doses on q8-12h intervals for 48 hours. Following a single IV dose, total body clearance and the steady-state volume of distribution averaged 3.3 ml/min/kg and 0.3L/kg, respectively. The mean-elimination half-life was 1.7 hours. In the urine, 60.4% of the administrated dose was recovered unchanged. Cefepime is mainly excreted via the kidneys and the mean renal clearance was 2.0ml/min/kg.

The mean plasmatic concentration of cefepime was identical following both single dose and multiple doses. Mild accumulation was seen. Other pharmacokinetic parameters were the same in infants and children after the initial dose and at steady state with a dosing interval of 8 or 12 hours. There were no pharmacokinetic significant effects of age or gender.

After IM injection, mean peak plasma levels of 68 μg/ml were reached after 0.75 hours.

Following IM injection, the mean trough steady- state concentration was 6.0 μg/ml after 8 hours. The absolute bioavailability of cefepime after an IM administration was 82.3%.

Average Cefepime Blood (P)/CSF Concentrations and ratio CSF/P in infants and children are listed in Table 8.

Table 8 Average Cefepime Blood (P)/CSF Concentrations and ratio CSF/P in infants and children*

Blood collection time	N	Blood (P) concentration (µg/ml)	CSF concentration (µg/ml)	Ratio CSF/P
0.5	7	67.1(51.2)	5.7(7.3)	0.12(0.14)
1	4	44.1(7.8)	4.3(1.5)	0.10(0.04)
2	5	23.9(12.9)	3.6(2.0)	0.17(0.09)
4	5	11.7(15.7)	4.2(1.1)	0.87(0.56)
8	5	4.9(5.9)	3.3(2.8)	1.02(0.64)

*The age range of patients is from 3.1 months until 12 years, with age average (SD) 2.6 (3.0) years. Patients with suspected CNS infection were treated with cefepime IV 50 mg/kg q8h over 5-20 minutes. Blood and CSF samples were taken from selected patients the 2nd or 3rd day of therapy, after the completion of IV infusion.

5.3 Preclinical safety data

Although no long term animal studies have been performed to evaluate carcinogenic potential, in vivo and in vitro testing has shown that cefepime is not genotoxic. Studies in rats have shown that there is no impact on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

L-arginine

6.2. Incompatibilities

Solutions of cefepime, like those of most beta-lactam antibiotics, must not be mixed either in injection syringe or in infusion set with the following antibiotics: metronidazole, vancomycin, gentamicin, tobramycin sulphate, because physical or chemical incompatibilities may arise. Should concomitant therapy be indicated, such agents must be administrated separately.

Intravenous:

Deltacef (cefepime hydrochloride for injection) is compatible at concentrations between 1-40mg/ml with the following IV infusion fluids: 5%w/v and 10%w/v Dextrose injection, 0.9 % w/v Sodium Chloride injection, Sodium Chloride 0.9% w/v and 5% Dextrose Intravenous Infusion and Ringer Lactate solution

Intramuscular:

Deltacef constituted with the following diluents: Sterile Water for Injection, 0,9% Sodium Chloride for Injection, 5% Dextrose for Injection, Sterile Bacteriostatic Water for Injection, or 1% Lidocaine Hydrochloride

Note: parenteral drugs should be inspected visually for particulate matter prior administration.
As with other cephalosporins, the colour of cefepime powder, as well as its solutions, tends to darken depending on storage conditions; however, when stored as recommended, the product potency is not adversely affected.

6.3. Shelf life

2 years
Reconstituted product:

Solution for IV Infusion: Cefepime powder for solution for injection is stable for up to 24 hours if stored at a temperature below 25^{o}C or up to 7 days in a refrigerator (2°C-8°C) with the following IV infusion fluids: 5%w/v and 10%w/v Dextrose injection, 0.9 % w/v Sodium Chloride injection, Sodium Chloride 0.9% w/v and 5% Dextrose Intravenous Infusion and Ringer Lactate solution.

Solution for IM Injection: Cefepime powder for solution for injection is stable for up to 24 hours if stored at a temperature below 25^{o}C or up to 3 days in refrigerator (2°C-8°C) with the following diluents: sterile water for injection, sterile bacteriostatic water for injection, 0.9 % w/v Sodium Chloride Injection, 5% w/v Dextrose Injection, and 1% w/v Lidocaine.

From a microbiological point of view, unless the method of opening and reconstitution precludes the risk of microbial contamination, the product should be used immediately. Once opened, the product may be stored for a maximum of 24 hours at 5°C ± 2°C.

6.4. Special precautions for storage

Store below 30°C, in the original packaging.
Reconstituted product: For storage conditions, see section 6.3.

6.5. Nature and contents of container

Deltacef 500 mg powder for injection or infusion: clear type I glass vials, nominal capacity 15 ml sealed with rubber stopper and aluminium caps, labelled, and packed in a card carton.
Deltacef 1 g powder for injection or infusion: clear type I glass vials, nominal capacity 15 ml sealed with rubber stopper and aluminium caps, labelled, and packed in a card carton.
Deltacef 2 g powder for injection or infusion: clear type I glass vials, nominal capacity 20 ml sealed with rubber stopper and aluminium caps, labelled, and packed in a card carton.

Pack size for all strengths: boxes of 1 vial, 10 vials, 50 vials and 100 vials.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Medochemie Ltd, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBERS

500mg: 21568
1g: 21569
2g: 21570

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01.11.2012 / 22/05/2019

10. DATE OF REVISION OF THE TEXT

22/05/2019