Cefepime
Core Safety Profile

4.3 Contraindications

-Cefepime is contraindicated in patients who have had previous hypersensitivity reactions to any component of the formulation, the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.

4.4 Special warnings and precautions for use

Warnings
In patients with impaired renal function, such as reduction of urinary output because of renal insufficiency (creatinine clearance ≤ 50 mL/min) or other conditions that may compromise 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 should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms (see sections 4.2 - Posology and method of administration and 5.2 - Pharmacokinetic properties). During postmarketing surveillance, the following serious adverse events have been reported: reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures (including nonconvulsive status epilepticus), and/or renal failure (see section 4.8 - Undesirable effects). 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 hemodialysis, however, some cases included a fatal outcome.

Special precautions for use
Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to cefepime occurs, discontinue the drug and treat the patient appropriately. Serious hypersensitivity reactions may require epinephrine and other supportive therapy.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cefepime, and may range in severity from mild diarrhea to fatal colitis. CDAD must be considered in all patients who present with diarrhea following antibiotic 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 antibiotic use not directed against *C. difficile* may need to be discontinued.

Renal function should be monitored carefully if drugs with nephrotoxic potential, such as aminoglycosides and potent diuretics are administered with cefepime.

As with other antibiotics, use of cefepime may result in overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Geriatric use
Of the more than 6400 adults treated with cefepime e in clinical studies, 35 % were 65 years or older while 16% were 75 years or older. For geriatric patients in clinical studies, when geriatric patients who received the usual recommended adult dose, clinical efficacy and safety were comparable to clinical efficacy and safety in non-geriatric adult patients, unless the patients had renal insufficiency. There was a

modest prolongation in elimination half-life and lower renal clearance values compared to those seen in younger persons. Dosage adjustments are recommended if renal function is compromised (see section 4.2 - Posology and administration and 5.2- Pharmacokinetic properties).
Cefepime 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 (see sections 4.8 Undesirable effects and 5.2 - Pharmacokinetic properties). Serious adverse events, including reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures (including nonconvulsive status epilepticus), and/or renal failure have occurred in geriatric patients with renal insufficiency given the usual dose of cefepime (see section 4.8 - Undesirable effects).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
Positive Coombs' test without hemolysis was detected in patients receiving cefepime two times daily (see section 4.8).
The result of glucose determination from urine may be false positive therefore glucose oxidase method is suggested.

4.6 Pregnancy and lactation

Pregnancy
Reproductive studies in mice, rats, and rabbits showed no evidence of fetal damage, however there are no adequate and well-controlled studies 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 in very low concentrations. Caution should be used when cefepime is administered to a nursing woman.

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 Special warnings and precautions for use, 4.8 Undesirable effects and 4.9 Overdose).

4.8 Undesirable effects

The table below includes all adverse events as currently listed in the CCDS†. The list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to ≤1/100), rare (≥1/10000 to ≤1/1000), very rare (≤ 1/10000), and not known (cannot be estimated from the available data).

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

TABLE 3 Adverse drug events reported during clinical or postmarketing experience

System Organ Class	Frequency	MedDRA Term

Infections and infestations	Uncommon Rare	Oral candidiasis, vaginal infection Candidiasis
Blood and lymphatic system disorders	Very common Common Uncommon Not known	Coombs test positive Prothrombin time prolonged, partial thromboplastin time prolonged, anaemia, eosinophilia Thrombocytopenia, leukopenia, neutropenia Aplastic anaemia[a], haemolytic anaemia[a], agranulocytosis
Immune system disorders	Rare Not known	Anaphylactic reaction Anaphylactic shock
Metabolism and nutrition disorders	Not known	Urine glucose false positive
Psychiatric disorders	Not known	Confusional state, hallucination
Nervous system disorders	Uncommon Rare Not known	Headache Convulsion, paraesthesia, dysgeusia, dizziness Coma, stupor, encephalopathy, altered state of consciousness, myoclonus
Vascular disorders	Common Rare Not known	Infusion site phlebitis Vasodilation Haemorrhage[a]
Respiratory, thoracic and mediastinal disorders	Rare	Dyspnoea
Gastrointestinal disorders	Common Uncommon Rare Not known	Diarrhoea Pseudomembranous colitis, colitis, nausea, vomiting Abdominal pain, constipation Gastrointestinal disorder
Hepatobiliary disorders	Common	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased
Skin and subcutaneous tissue disorders	Common Uncommon Not known	Rash Erythema, urticaria, pruritus Toxic epidermal necrolysis[a] , Stevens-Johnson syndrome[a], erythema multiforme[a]
Renal and urinary disorders	Uncommon Not known	Blood urea increased, blood creatinine increased Renal failure, nephropathy toxic[a]
Reproductive system and breast disorders	Rare	Pruritus genital
General disorders and administration site condition	Common Uncommon Rare	Infusion site reaction, injection site pain, injection site inflammation Pyrexia, infusion site inflammation Chills
Investigations	Common	Alkaline phosphatase increased

~~a:~~[a] Adverse reactions that are generally accepted as being attributable to other compounds in the class.

Pediatrics
The safety profile of ~~-~~cefepime in infants and children is similar to that seen in adults. The most frequently reported adverse event considered related to cefepime in clinical trials was rash.

4.9 Overdose

In case of severe overdosage, especially in patients with compromised renal function, hemodialysis will aid in the removal of cefepime from the body; peritoneal dialysis is of no value. Accidental overdosing has occurred when large doses were given to patients with impaired renal function (see sections 4.2 - Posology and administration and 4.4 - Special warnings and precautions for use). Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures~~, and neuromuscular excitability~~ (see section 4.8).

Pripombe dodal [l1]: It is likely that the term "neuromuscular excitability" was included as an adverse reaction in the Overdosage section of the Maxipime SmPC for Slovenia as an inclusive term for the events of myoclonus and seizures. This occurred when the cefepime Company Core Data Sheet (CCDS) was revised in August 2000 to add post-marketing reports of adverse reactions in patients with renal impairment. Our recent review of the Safety database for cefepime revealed no reports of "neuromuscular excitability" associated with the use of cefepime. Therefore, BMS recommends that this ADR be removed from the Maxipime SmPC for Slovenia. BMS intends to revise the cefepime CCDS to reflect this change.