MAXIPIME 500 mg/1.5 mL powder and solvent for injectable solution
MAXIPIME 1000 mg/3 mL powder and solvent for injectable solution
MAXIPIME 2000 mg/10 mL powder and solvent for injectable solution
cefepime

PHARMACOTHERAPEUTIC CATEGORY
MAXIPIME is an antibiotic.

THERAPEUTIC INDICATIONS
MAXIPIME is indicated in the treatment of moderate and severe infections in adults caused by susceptible strains of bacteria, among which respiratory tract infections, lower and upper urinary tract infections (complicated and non-complicated), skin and soft tissue infections, intra-abdominal infections, including peritonitis and biliary infections, septicemia/bacteremia, including febrile episodes in patients with compromised immune systems.
MAXIPIME is indicated in the treatment of children for cerebrospinal meningitis sustained by susceptible germs.
MAXIPIME is indicated in the treatment of infections caused by one or more susceptible strains, aerobic and anaerobic.
For this wide antibacterial spectrum, after having obtained the results of the susceptibility test, MAXIPIME can be used alone as the first choice drug. When necessary, MAXIPIME can be used safely in association with aminoglycoside antibiotics or with other antibiotics.
MAXIPIME is indicated in surgical prophylaxis in patients that undergo intra-abdominal surgery.

CONTRAINDICATIONS
Hypersensitivity to the active principle or any of the excipients, cephalosporins, penicillins or other beta-lactam antibiotics

PRECAUTIONS FOR USE
In patients with impaired renal function, such as reduced diuresis caused by renal insufficiency (creatinine clearance ≤ 50 mL/min) or other conditions that may compromise renal function, the dose of MAXIPIME must be adjusted to compensate for the diminished renal elimination. Due to the fact that elevated or prolonged antibiotic serum concentrations occur at normal dose levels in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dose must be reduced when Cefepime is administered to these patients. Repeated doses must be determined on the basis of the level of impaired renal function, the severity of the infection and the susceptibility of the etiological agent (see Dosage, method and timing of administration). During the post-marketing evaluation, the following severe adverse events have been reported: reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures (including non-convulsive epileptic states), and/or renal insufficiency (see Undesired effects). Most of the cases were reported in patients with impaired renal function that received doses of MAXIPIME above those recommended. In general, symptoms of neurotoxicity have disappeared after the discontinuation of Cefepime and/or hemodialysis; however, the outcome of some cases has been fatal.
As with other beta-lactam antibiotics, before beginning therapy with MAXIPIME, careful inquiry must be made to determine whether or not the patient has had prior hypersensitive reactions to penicillins or other drugs; if the answer is affirmative, MAXIPIME must be administered with extreme caution.
When an allergic reaction to MAXIPIME occurs, therapy must be discontinued and the patient appropriately treated. Severe reactions of hypersensitivity may require adrenaline and supportive measures.
Diarrhea associated with *Clostridium difficile* that ranges in severity from mild diarrhea to fatal colitis has been reported with the use of all anti-bacterial agents including MAXIPIME. Therefore, it is important to take into consideration the diagnosis of C. *difficile* associated with diarrhea in all patients that have diarrhea following antibiotic therapy. A precise clinical case history is necessary since the onset of diarrhea associated with C. *difficile* can occur also in the two months following the administration of anti-bacterial agents.
In case of suspected or confirmed C. *difficile*, it may be necessary to interrupt the antibiotic therapy not prescribed for this pathology.
In case of concomitant use of drugs that are potentially nephrotoxic such as aminoglycosides and potent diuretics, renal function must be controlled carefully.

Elderly patients
Of the more than 6400 adult patients treated with MAXIPIME in clinical studies, 35% were 65 years or older while 16% were 75 or older. In clinical studies, elderly patients being treated with doses commonly recommended for adults have demonstrated clinical efficacy and safety comparable to those in adult patients, unless the patients had renal insufficiency. The differences are limited to a modest prolongation of the half-life and a lower renal clearance compared to the younger patients. If the renal function is impaired, it is recommended to adjust the dose (see Dose, method and timing of administration).
It is known that Cefepime is excreted mainly through the kidneys and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Given that elderly patients are more susceptible to decreased renal function, it is important to be careful in choosing the dose and in monitoring renal function (see Undesired effects). Geriatric patients with renal insufficiency who were administered normal doses of Cefepime showed serious adverse events such as reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures (including non-convulsive epileptic states), and/or renal insufficiency (see Undesired effects).

INTERACTIONS
Positive reactions to the direct Coombs test, without evidence of hemolysis, have been observed in 12.3% of patients that received MAXIPIME every 12 hours during clinical studies.
In patients treated with MAXIPIME, false positive reactions of glycosuria in the urine have occurred when using reducing agents. False positive reactions have not been observed with methods that include glucose-oxidase.

SPECIAL WARNINGS
Pregnancy and nursing
The safety of MAXIPIME has not been established in pregnant women because adequate well-controlled studies have not been carried out on these patients.
Studies on reproduction carried out on animals with doses up to 8 to 10 times the maximum daily dose do not indicate direct or indirect damaging effects on reproduction, embryonic or fetal development, the gestation period and peri- and post-natal development. Since studies on animal reproduction are not always predictive of the response in humans, it is recommended to use the drug only when strictly necessary during pregnancy.
Cefepime is excreted in very low concentrations in human breast milk; therefore, caution must be used when administering the drug to a woman that is nursing.

Effects upon driving and use of machinery
No studies have been conducted on the capacity of driving vehicles or using machinery.

DOSAGE, METHODS AND TIMING OF ADMINISTRATION

MAXIPIME can be administered by intravenous or intramuscular injection.
When administered alone by intramuscular injection, MAXIPIME generally does not cause pain.
The dose and means of administration vary according to the susceptibility of the organism in question, the severity of the infection, renal function and general conditions of the patient.

Adults
A guide for Cefepime doses for adults and children older than 12 years of age with normal renal function is given in chart 1.
Administration by intravenous injection is preferable for patients with severe infections especially when the infection is life-threatening, especially if septic shock occurs.

Chart 1
*Adults and children older than 12 years of age with normal renal function **

Type of infection	Dose and means of administration	Interval
Urinary tract infections (UTI)	500 mg - 1 g IV or IM	every 12h
Non-urinary tract infections	1 g IV or IM	every 12h
Severe infections	2 g IV	every 12h
Very severe infections (life-threatening)	2 g IV	every 8h

* The duration of the therapy normally varies between 7 to 10 days; more severe infections may require longer treatment. The empiric therapy of febrile neutropenia (patients with compromised immune systems) must last seven days or until the neutropenia is resolved.

Surgical prophylaxis (adults): the recommended doses for the prevention of bacterial infections during or after surgical operations are the following:

- A single dose of 2 g IV of MAXIPIME (infusion of 30 minutes, see "Instructions for use") to begin 60 minutes before the surgical operation. A single dose of 500 mg IV of metronidazole, if deemed necessary, may be administered immediately after the end of the infusion of MAXIPIME. The dose of metronidazole must be prepared and administered according to the technical information of the product. Because of the incompatibility of MAXIPIME and metronidazole, they must not be mixed in the same container; it is recommended to wash the deflux device with compatible liquid before administering metronidazole.
- If the duration of the operation exceeds 12 hours, a second dose of MAXIPIME followed by metronidazole, if necessary, must be administered 12 hours after the initial prophylactic dose.

Children between the ages of one month in 12 years with normal renal function
Bacterial meningitis
Recommended dose: patients over two years of age weighing ≤ 40 kg: 50 mg/kg every 8 hours for 7 - 10 days.
Experience with the use of MAXIPIME in patients less than two months of age is limited. While this experience was obtained at 50 mg/kg, the pharmacokinetic data obtained on individuals older than two months suggests a dose of 30 mg/kg every 12 or 8 hours can be considered adequate in pediatric patients between the first and second month of life. The doses of 30 mg/kg between the first and second months and those of 50 mg/kg between two months and 12 years are comparable to a dose of 2 g in an adult. The administration of MAXIPIME in these patients must be carefully controlled.
For pediatric patients weighing more than 40 kg, the dose scheme for adults can be applied (see Chart 1). For patients older than 12 years of age weighing ≤ 40 kg, the scheme for the younger patients weighing ≤ 40 kg must be used.
The pediatric dose must not exceed the dose for adults (2 g every 8 hours). Experience in intramuscular administration in pediatric patients is limited.

Elderly patients
No adjustment of doses is required except in cases of concomitant renal insufficiency (see Necessary precautions of use).

Impaired hepatic function
No adjustment of doses is required except in cases of concomitant renal insufficiency.

Impaired renal function
In patients with impaired renal function, the dose of Cefepime must be adjusted in order to compensate for the diminished renal elimination. The recommended initial dose of Cefepime in patients with mild to moderate impaired renal function must be the same as patients with normal renal function. The recommended maintenance dose of Cefepime in patients with impaired renal function is indicated in the following chart.

Chart 2
Maintenance dosage in adults with renal insufficiency*

Creatinine Clearance (mL/min)	*Recommended maintenance dosage*			
> 50	(normal dosage, no adjustment) 2 g every 8h	2 g every 12h	1 g every 12h	500 mg every 12h
30 - 50	2 g every 12h	2 g every 24h	1 g every 24h	500 mg every 24h
11 - 29	2 g every 24h	1 g every 24h	500 mg every 24h	500 mg every 24h
≤ 10	1 g every 24h	500 mg every 24h	250 mg every 24h	250 mg every 24h
Hemodialysis *	500 mg every 24h	500 mg every 24h	500 mg every 24h	500 mg every 24h

* Pharmacokinetic modeling indicates that a reduced dose is necessary for these patients.
Patients that receive Cefepime and at the same time undergo hemodialysis must receive the following dosage: a loading dose of 1 g the first day of therapy with Cefepime and, subsequently, 500 mg a day. On days of dialysis, Cefepime must be administered immediately afterwards. When possible, Cefepime must be administered at the same time every day

Patients undergoing hemodialysis
In patients undergoing hemodialysis, about 68% of the total quantity of Cefepime present in the organism at the beginning of dialysis will be eliminated during a period of three hours. At the end of each dialysis treatment, a dose equal to the initial dose must be administered.
In patients undergoing continuous peritoneal dialysis, MAXIPIME may be administered at normally recommended doses for patients with normal renal function (in other words, 500 mg, 1 g or 2 g depending on the severity of the infection) but at a dosage interval of every 48 hours
Pediatric patients with impaired renal function
Given that urinary excretion is the principal route of eliminating Cefepime, it is recommended to adjust the dose in pediatric patients with impaired renal function.
As recommended in chart 2, the same increments of intervals between doses and/or a reduction of the latter must be used.

Duration of treatment
The duration of the therapy depends on the course of the infection and must therefore be established by the physician.

Instructions for use
Intravenous administration
For preparing the solution of MAXIPIME to be administered intravenously, the following diluents must be used:
- Water for injectable preparations F.U.
- Physiological saline solution (solution of sodium chloride at 0.9%), with or without 5% of glucose
- Ringer solution with or without 5% of glucose
- Glucose solution at 5% or 10%
- 6 M Sodium lactate solution

MAXIPIME can be slowly injected into the vein in a period of three to five minutes. The drug can also be administered directly through perfusion tubes or through continuous intravenous infusion. When administering by infusion, inject the drug within approximately 30 minutes.

Intramuscular administration
MAXIPIME 0.5 g is diluted with 1.5 mL of sterile water for injectable preparations (supplied in the package).
MAXIPIME 1 g is diluted with 3 mL of sterile water for injectable preparations (supplied in the package
Reconstitution volumes
The reconstitution volumes of MAXIPIME for intravenous and intramuscular administration are summarized in the following chart:

CHART 3
Instructions for reconstitution

Vial	Diluent volume (mL)	Concentration obtained (mg/mL)
0.5 g IM	1.5	230
0.5 g IV	5.0	90
1 g IM	3.0	230
1 g IV	10.0	90
2 g IV	10.0	160

The solution must be reconstituted at the time of use.
It is preferable to administer the drug immediately after its reconstitution.
MAXIPIME can be administered contemporaneously with other antibiotics or other drugs as long as they are not mixed in the same syringe or perfusion liquid.
As with other cephalosporins, the MAXIPIME solutions can vary in colorization depending on the period of conservation. This characteristic has no influence on the efficacy and tolerability of the drug.

OVERDOSAGE
In case of severe overdosage, especially in patients with impaired renal function, the serum levels of MAXIPIME can be reduced with hemodialysis. Peritoneal dialysis does not help. Accidental overdosage can occur when large doses of the drug are taken by patients with impaired renal function (see Dosage, method and timing of administration, Necessary precautions for use, Undesired effects).
Symptoms of overdosage include encephalopathy, myoclonus, seizures and neuromuscular excitability.
In case of an accidental overdose of the medicine, immediately notify your physician or contact the nearest hospital.

UNDESIRED EFFECTS
MAXIPIME is generally well tolerated.
In clinical studies (N=5598), the most common adverse events were gastrointestinal symptoms and hypersensitivity reactions.
The adverse reactions rarely required discontinuing treatment and were mild and transitory in nature. The following is a list of adverse reactions during therapy with MAXIPIME considered correlated with the drug:
Adverse reactions reported with an incidence between 0.1 and 1% (if not otherwise specified)
Hypersensitivity: skin rash (1.8%), itching, urticaria and fever.
Digestive system: nausea, vomiting, oral candidiasis, diarrhea (1.2%), colitis (including pseudomembranous colitis).
Central nervous system: headache
Other: fever, vaginitis, erythema.
Adverse reactions reported with an incidence between 0.05 and 0.1%: abdominal pain, constipation, vasodilatation, dyspnea, dizziness, paraesthesia, genital itching, alteration of taste, chills, nonspecified candidosis.
Clinically significant events occurring in less than 0.05% of cases included anaphylaxis and seizures.
Local reactions
At the site of IV infusion (5.2%): phlebitis (2.9%) and inflammation (0.1%).
In the area of intramuscular injection: pain and inflammation (2.6%)

Alteration of laboratory parameters that developed during clinical trials in patients with normal base values was transitory. Those that occurred with an incidence of 1-2% (if not specified otherwise) were the following: anemia, eosinophilia, thrombocytopenia (0.5-1%), positive Coombs test without hemolysis (18.7%), increase in transaminase (ALT 3.6%; AST 2.5%), alkaline phosphatase, total bilirubinemia, azotemia (0.5-1%), creatininemia (0.5-1%), prothrombin time and partial thromboplastin time (2.8%). Rare cases of leukopenia and neutropenia were observed and were transitory.
The following were also reported: anaphylaxis (including anaphylactic shock), transitory leukopenia, neutropenia, agranulocytosis and thrombocytopenia.
Pediatric patients: the safety profile in children is similar to that observed in adults with rash being the most frequently reported event in the clinical studies.
From post-marketing clinical experience, the following events have been reported for which, however, it has not been possible to determine a cause-effect relationship with the drug: as with other drugs in this class, encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), seizures, and myoclonus, and/or renal insufficiency. Most of the cases were reported in patients with impaired renal function who received doses greater than those recommended (see Necessary precautions of use).
Carefully following the instructions in this insert will reduce the risk of undesired effects.
The patient must inform his physician or pharmacist of any undesired effect even if it is not described in this insert.

EXPIRATION AND STORAGE

See the expiration date indicated on the package. This date refers to an unopened package, properly stored.
Special precautions for the storage of the medicine
Keep away from light.
Warning: do not use the medicine after the expiration date indicated on the package.
Medicines must not be flushed down the drain or thrown away in the trash. Ask your pharmacist for information on the disposal of medicine you no longer use.
KEEP THE MEDICINE OUT OF THE SIGHT AND REACH OF CHILDREN.

COMPOSITION

MAXIPIME 500 mg/1.5 mL powder and solvent for injectable solution
Each vial contains
Active principle: Cefepime dihydrochloride monohydrate, equal to 500 mg of cefepime
Excipients: L-arginine.
MAXIPIME 1000 mg/3 mL powder and solvent for injectable solution
Each vial contains
Active principle: Cefepime dihydrochloride monohydrate, equal to 1000 mg of cefepime
Excipients: L-arginine.
MAXIPIME 2000 mg/10 mL powder and solvent for injectable solution
Each vial contains
Active principle: Cefepime dihydrochloride monohydrate, equal to 2000 mg of cefepime
Excipients: L-arginine.

Each vial of solvent contains:
water for injectable preparations

PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for injectable solution for intramuscular or intravenous use.
Package of one 500 mg vial + one 1.5 mL vial of solvent; one 1000 mg vial + one 3 mL vial of solvent; one 2000 mg vial + one 10 mL vial of solvent.

PROPRIETOR of MARKETING AUTHORIZATION

Bristol-Myers Squibb S.r.l., via del Murillo km 2.800 – Sermoneta (LT)

MANUFACTURER

Bristol-Myers Squibb S.r.l., via del Murillo km 2.800 – Sermoneta (LT)
Vials of solvent also manufactured in the following plant
BRISTOL-MYERS SQUIBB S.r.l., Località Fontana del Ceraso - Anagni (FR)

REVISION OF INSERT BY THE ITALIAN DRUG AGENCY: September 2008.