# Part II

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Kefadol 1.0g Powder for Solution for Injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1000 mg (1 g) of cefamandole (as cefamandole nafate).

For excipients, see 6.1.

## 3 PHARMACEUTICAL FORM

Powder for solution for injection
A white to off-white, sterile, crystalline powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Cefamandole is indicated in the treatment of infections of the lower respiratory tract, genito-urinary tract, bones and joints, bloodstream (septicaemia), skin and soft tissue, gall bladder and peritoneum, and pelvic inflammatory disease in women, when due to susceptible micro-organisms.

Prophylactic use: Perioperative administration of cefamandole may reduce the incidence of postoperative infections in patients undergoing contaminated or potentially contaminated surgical procedures associated with a high risk of infection, or where the occurrence of a postoperative infection could be especially serious.

### 4.2 Posology and method of administration

Cefamandole nafate may be given intravenously or by deep intramuscular injection into a large muscle mass to minimise pain.

Adults and the elderly:
The dosage range for cefamandole is 500mg to 2g every four to eight hours, depending on the severity and site of infection.

Impaired renal function:
When renal function is impaired, a reduced dosage must be employed and serum concentrations should be monitored when feasible.
After an initial dose of 1 to 2g (depending on the severity of infection), a maintenance dosage schedule should be followed (see table). Continued dosage should be determined by degree of renal impairment, severity of infection and susceptibility of the causative organism.

**Maintenance Dosage of Cefamandole in Patients with Impaired Renal Function.**

| **CREATININE CLEARANCE ml/min/1.73m$^2$** | **LIFE-THREATENING INFECTIONS** | **SEVERE INFECTIONS** | **LESS SEVERE INFECTIONS** |
|---|---|---|---|
| 80-50 | 2g q 6h | 1.5g q 6h | 0.75g q 6h |
| 50-25 | 2g q 8h | 1.5g q 8h | 0.75g q 8h |
| 25-10 | 1.25g q 8h | 1.0g q 8h | 0.5g q 8h |
| 10-2 | 1g q 12h | 0.75g q 12h | 0.5g q 12h |
| <2 | 0.75g q 12h | 0.5g q 12h | 0.25g q 12h |

Intramuscular administration:
Each gram of cefamandole should be reconstituted with 3 ml of Water for Injections Ph. Eur or Sodium Chloride Intravenous Infusion BP. Shake well until dissolved.

Intravenous administration:
Intravenous route may be preferable for bacterial septicaemia, localised parenchymal abscesses, peritonitis, or other severe or life-threatening infections.

1. *For direct intermittent intravenous administration*, each gram of cefamandole should be reconstituted with 10ml of Water for Injections Ph. Eur, 5% Dextrose Intravenous Infusion BP, or Sodium Chloride Intravenous Infusion BP. Slowly inject directly into the vein over a period of three to five minutes or give through the tubing of an administration set while the patient is also receiving one of the following intravenous fluids:

Sodium Chloride Intravenous Infusion BP.
5% Dextrose Intravenous Infusion BP.
10% Dextrose Intravenous Infusion BP.
5% Dextrose and 0.9% Sodium Chloride Intravenous Infusion BP.
5% Dextrose and 0.45% Sodium Chloride Intravenous Infusion BP.
Sodium Lactate Intravenous Infusion BP.

2. *Intermittent intravenous infusion with a Y-type administration set or volume control set* can also be accomplished while any of the above mentioned intravenous fluids are being infused. However, during infusion of the solution containing cefamandole, it is desirable to discontinue the other solution. When this technique is employed, careful attention should be paid to the volume of the solution containing cefamandole so that the calculated dose will be infused. When a Y-tube connection is used, 100ml of an appropriate diluent should be added to 2g cefamandole.

If Water for Injections Ph. Eur is used as the diluent, reconstitute with approximately 20ml per g to avoid a hypotonic solution.

3. *For continuous intravenous infusion*, each gram of cefamandole should be diluted with 10ml of Water for Injections Ph. Eur. An appropriate quantity of the resulting solution may be added to an IV bottle containing one of the previously mentioned intravenous fluids.

If combination therapy with cefamandole and an aminoglycoside is indicated, each of these should be administered at separate sites.

Infants and children:
Administration of 50 to 100mg/kg/day in equally divided doses every four to eight hours has been effective for most infections susceptible to cefamandole. This may be increased to a total daily dose of 150 mg/kg (not to exceed the maximum adult dose) for serious infections.

Infants:
Cefamandole has been effectively used in this age group, but all laboratory parameters have not been extensively studied in infants between 1 and 6 months of age. Safety of this product has not been established in premature and infants under 1 month of age; therefore, if cefamandole is to be administered to infants, the physician should determine whether the potential benefits outweigh the possible risks involved. Accumulation of cephalosporins (with resulting prolongation of drug half-life) has been reported in neonates.

Prophylactic use:
The following schedules are recommended for perioperative use.

Adults and the elderly:
1 or 2g intravenously or intramuscularly one-half to one hour prior to surgical incision, followed by 1 or 2g every six hours for 24-48 hours.

For patients undergoing procedures involving implantation of prosthetic devices, administration for up to 72 hours is recommended.

Children (more than three months of age):
50-100mg/kg/day in equally divided doses by the same routes and schedules designated for adults.

If signs of infection occur, cultures should be obtained and appropriate therapy instituted.

Kefadol should be continued for a minimum of 48 to 72 hours after the patient becomes asymptomatic or bacterial eradication has occurred. A minimum of 10 days treatment is recommended in infections caused by group A beta-haemolytic streptococci. In chronic urinary tract infection, frequent bacteriological and clinical appraisal is necessary during therapy and possibly for several months after completion. Persistent infections may require treatment for several weeks.

## 4.3 Contraindications

Cefamandole is contra-indicated in patients with known allergy to the cephalosporin group of antibiotics.

## 4.4 Special warnings and precautions for use

*Warnings*

Before cefamandole therapy is instituted, careful enquiry should be made concerning previous hypersensitivity reactions to cephalosporins, penicillins or other drugs. Kefadol should be given cautiously to penicillin-sensitive patients.
There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with most broad-spectrum antibiotics. Its diagnosis should be considered in patients who develop diarrhoea with antibiotics. Such colitis may range from mild to life-threatening.

*Precautions*

Although cefamandole rarely produces alteration in kidney function, evaluation of renal status is recommended, especially in seriously ill patients receiving maximum doses. Patients with impaired renal function should be placed on the dosage schedule recommended under 'Posology and Method of Administration'. Usual doses in such individuals may result in excessive serum concentrations.

As with other broad-spectrum antibiotics, hypoprothrombinaemia with or without bleeding has been reported rarely,

but it has been promptly reversed by administration of vitamin K. Such episodes have usually occurred in elderly, debilitated or otherwise compromised patients with deficient stores of vitamin K. Prophylactic administration of vitamin K may be indicated in such patients, especially when intestinal sterilisation and surgical procedures are performed.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastro-intestinal disease, particularly colitis.

Prolonged use of cefamandole may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

*Impairment of fertility*: Very high doses of cefamandole (equivalent to approximately 5 times the maximum clinical dose) have been found to delay maturation of the testicular germinal epithelium in rats. This effect was seen only when cefamandole was given to neonatal rats during initial spermatogenic development. The clinical significance of this finding is unknown due to differences in the time of initiation of spermatogenesis, rate of spermatogenic development and duration of puberty.

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

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

The result of experimental studies in animals suggest that the concurrent use of potent diuretics such as frusemide or ethacrynic acid may also increase the risk of renal toxicity with cephalosporin antibiotics.

In a few patients receiving cefamandole, nausea, vomiting and vasomotor instability with hypotension and peripheral vasodilatation, has occurred following the ingestion of alcohol. Cefamandole inhibits the enzyme acetaldehyde dehydrogenase in laboratory animals. This causes accumulation of acetaldehyde when ethanol is administered concurrently.

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with Clinitest tablets. A false positive test for proteinuria may occur with acid and denaturisation precipitation tests.

## 4.6 Pregnancy and lactation

*Usage in pregnancy:* Reproduction studies in rats given doses of 500 or 1000mg/kg/day (approximately 5 times the maximum clinical dose) revealed no evidence of impaired fertility or harm to the foetus due to cefamandole nafate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

*Nursing mothers:* Caution should be exercised.

## 4.7 Effects on ability to drive and use machines

None known.

## 4.8 Undesirable effects

*Hypersensitivity:*
Anaphylaxis, maculopapular rash, urticaria, eosinophilia and drug fever have been reported. These reactions are more likely to occur in patients with a history of allergy, particularly to penicillin.

*Haematological:*
Thrombocytopenia has been reported rarely. Neutropenia has been reported, especially in long courses of treatment. Some individuals have developed positive direct Coombs' tests during treatment with the cephalosporin antibiotics.

*Gastro-intestinal:*
Nausea and vomiting occur rarely. Colitis, including rare instances of pseudomembranous colitis, has been reported.

*Liver*:
Transient rise in AST, ALT and ALP levels have been noted. Transient hepatitis and cholestatic jaundice have been reported rarely.

*Kidney:*
Decreased creatinine clearance has been reported in patients with prior renal impairment.

As with some other cephalosporins, transitory elevations of blood urea have occasionally been observed; their frequency increases in patients over 50 years of age. In some of these cases, there was also a mild increase in serum creatinine.

*Local reactions:*
Pain on intramuscular injection if infrequent.
Thrombophlebitis occurs rarely.

## 4.9 Overdose

The administration of inappropriately large doses of parenteral cephalosporins may cause seizures, particularly in patients with renal impairment. Dosage reduction is necessary when renal function is impaired (see 'Posology and Method of Administration').

If seizures occur, the drug should be promptly discontinued; anticonvulsant therapy may be administered if clinically indicated.

In the event of serious overdosage, general supportive care is recommended, with monitoring of haematological, renal and hepatic functions, and coagulation status, until the patients is stable. Haemodialysis may be considered in cases of overwhelming overdosage.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Cefamandole is a semi-synthetic broad-spectrum cephalosporin antibiotic. The bacterial action of cefamandole results from inhibition of cell-wall syntheses.

Cefamandole is usually active against the following organisms *in vitro* and in clinical infections:

Gram-positive:

Staphylococci, including coagulase-positive, coagulase-negative (e.g., *Staphylococcus epidermidis*) and penicillinase-producing strains.

Beta-haemolytic and other streptococci (most strains of enterococci, e.g., *Enterococcus faecalis*, are resistant).

*Streptococcus pneumoniae*.

Gram-negative:

*Escherichia coli.*

Klebsiella spp.

Enterobacter spp. (initially susceptible organisms occasionally may become resistant during therapy).

*Haemophilus influenzae.*

*Proteus mirabilis.*

*Providencia rettgeri.*

*Morganella morganii.*

*Proteus vulgaris* (some strains of *P. vulgaris* have been shown by *in vitro* tests to be resistant to cefamandole and certain other cephalosporins).

Anaerobic organisms:

Gram-positive and gram-negative cocci (including Peptococcus and Peptostreptococcus spp.).

Gram-positive Bacilli (including Clostridium spp.).

Gram-negative bacilli (including Bacteroides).

Most strains of *Bacteroides fragilis* are resistant.

Pseudomonas, *Acinetobacter calcoaceticus* and most Serratia strains are resistant to cefamandole and certain other cephalosporins. Cefamandole is resistant to degradation by beta-lactamases from certain members of the Enterobacteriaceae.

## 5.2 Pharmacokinetic properties

After addition of a diluent, cefamandole nafate rapidly hydrolyzes to cefamandole, and both compounds have microbiologic activity *in vivo*. Peak plasma concentrations of 13 micrograms/ml and 25 micrograms/ml have been achieved 0.5 to 2 hours after intramuscular doses of 500mg and 1g respectively.

Following intravenous doses of 1, 2 and 3g, serum concentrations were 139, 240 and 533 micrograms/ml respectively at 10 minutes. These concentrations declined to 0.8, 2.2 and 2.9 micrograms/ml at 4 hours. Intravenous administration of 4g doses every 6 hours produced no evidence of accumulation in the serum. Plasma half-lives vary from about 0.5 to 1 hour depending on the route of infection. About 70% is bound to plasma proteins. The antibiotic reaches therapeutic levels in pleural and joint fluids and in bile and bone. Sixty-five to 85% of cefamandole is excreted by the kidneys within 8 hours resulting in high urinary concentrations.

Probenecid slows tubular excretion and doubles the peak serum level and the duration of measurable serum concentrations.

Accumulation of cephalosporins (with resulting prolongation of drug half-life) has been reported in neonates.

## 5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber in addition to that summarised in other sections of the Summary of Product Characterises.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium carbonate

## 6.2 Incompatibilities

Do not mix an aminoglycoside with cefamandole in the same intravenous fluid container. Formulations of cefamandole available for injection contain sodium carbonate and are incompatible with solutions containing calcium or magnesium salts.

## 6.3 Shelf Life

*Unreconstituted vials:* Three years.

*Reconstituted vials:* Chemical and physical in-use stability has been demonstrated for 24 hours at 4°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer not be longer than 24 hours at 2°C to 8°C.

## 6.4 Special precautions for storage

*Unreconstituted vials:* Do not store above 25°C. Keep container in the outer carton.

*Reconstituted vials:* See 6.3.

## 6.5 Nature and contents of container

A 10 ml, clear colourless, Type III Ph. Eur. glass vial. Single vial.

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Kefadol should be inspected visually for particulate matter and any abnormal discolouration. Solutions of Kefadol range from light yellow to amber, depending on a variety of factors, including concentration and the diluent used.

The pH of freshly reconstituted solutions usually ranges from 6.0 to 8.5.

## 7 MARKETING AUTHORISATION HOLDER

Eli Lilly and Company Limited
Kingsclere Road
Basingstoke
RG12 6XA
England

## 8 MARKETING AUTHORISATION NUMBER

PA 47/38/3

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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## 10 DATE OF REVISION OF THE TEXT

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