Cefoperazone Injection I.P.
MAGNAMYCIN®

1. GENERIC NAME

Cefoperazone Injection I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains: Sterile Cefoperazone Sodium I.P. equivalent to Cefoperazone 250 mg, 1 g and 2 g.

Cefoperazone sodium is a semi-synthetic broad-spectrum cephalosporin antibiotic for parenteral use only. Cefoperazone contains 34 mg sodium (1.5 mEq) per gram. Cefoperazone is a white crystalline powder, which is freely soluble in water. The pH of a 25% aqueous solution is 5.0 to 6.5 and the solution is colorless to straw-yellow, depending on the concentration. The empirical formula is $C_{25}H_{26}N_9NaO_8S_2$.

All strengths/presentations mentioned in this document might not be available in the market.

List of Excipients

None

3. DOSAGE FORM AND STRENGTH

Sterile powder for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mono-therapy

Cefoperazone is indicated for the treatment of the following infections when caused by susceptible organisms:

Respiratory Tract Infections
Urinary Tract Infections
Intra-abdominal Infections (including biliary and pelvic)
Septicemia
Meningitis
Skin and Soft Tissue Infections
Infections of Bones and Joints
Gonorrhea

Prophylaxis

Cefoperazone sodium may be indicated in the prophylaxis of post-operative infection in patients undergoing abdominal and gynecological surgery, cardiovascular surgery, and orthopedic surgery.

Combination Therapy

Because of the broad spectrum of activity of cefoperazone, most infections can be treated adequately with this antibiotic alone. However, cefoperazone may be used concomitantly with other antibiotics if such combinations are indicated. If an aminoglycoside is used, renal function should be monitored during the course of therapy (see sections 4.2 Posology and method of administration and section 8.1 Incompatibilities).

4.2 Posology and method of administration

Administration in Adults

The usual adult daily dosage of cefoperazone is 2 to 4 grams per day administered in equally divided doses every 12 hours. In severe infections the dosage may be increased to a total of 8 grams per day in equally divided doses every 12 hours. Twelve grams per day have been administered in equally divided doses every 8 hours and usage of up to 16 grams per day in divided doses has been reported without complications. Treatment may be started before results of susceptibility testing are available.

The recommended dosage for uncomplicated gonococcal urethritis is 500 mg intramuscularly as a single dose.

The drug should be given by deep intramuscular injection into the large muscle mass of the gluteus maximus or anterior thigh.

Use in Hepatic Dysfunction

Dose modification may be necessary in cases of severe biliary obstruction, severe hepatic disease or coexistent renal dysfunction. In these cases dosage should not exceed 2 grams/day without close monitoring of serum concentrations.

Use in Renal Dysfunction

Since renal excretion is not the main route for the elimination of cefoperazone, patients with renal failure require no adjustment in dosing when usual dosages (2-4 grams daily) are administered. For patients whose glomerular filtration rate is less than 18 ml/min or whose serum creatinine level is greater than 3.5 mg/dl, the maximum dosage of cefoperazone should be 4 grams per day.

The serum half-life of cefoperazone is reduced slightly during hemodialysis. Thus dosing should be scheduled to follow a dialysis period.

Use in Patients with Hepatic and Concurrent Renal Dysfunction

In patients with hepatic dysfunction and concomitant renal impairment, cefoperazone serum concentrations should be monitored and dosage adjusted as necessary. In these cases dosage should not exceed 2 grams/day without close monitoring of serum concentrations.

Administration in Infants and Children

In infants and children, a 50 to 200 mg/kg/day dosage of cefoperazone should be given in divided doses every 8 to 12 hours. The maximum dose should not exceed 12 grams/day. (see section 4.4 Special warnings and precautions for use).

Use in Neonates

For neonates aged less than 8 days, the drug should be given every 12 hours.

Intravenous Administration in Adults and Children

For intermittent intravenous infusion, each 1 or 2 gram vial of cefoperazone should be dissolved in 20 to 100 ml of a compatible sterile intravenous solution and infused over a period of 15 minutes to one hour. If sterile water for injection is the preferred diluent, no more than 20 ml should be added to the vial.

For continuous intravenous infusion, each gram of cefoperazone should be dissolved in 5 ml of Sterile Water for Injection and the solution added to an appropriate intravenous diluent.

For direct intravenous injection, the maximum dose of cefoperazone should be two grams per administration for adults and 50 mg/kg per administration for children. The drug should be dissolved in an appropriate diluent to give a final concentration of 100 mg/ml and administered over a period of no less than three to five minutes.

For the antibiotic prophylaxis of surgical procedures, 1 or 2 grams should be administered intravenously 30 to 90 minutes prior to the start of surgery. The dose may be repeated every 12 hours, in most cases for no longer than 24 hours. In surgery where the incidence of infection is known to be greater (e.g., colorectal surgery) or when the occurrence of infection may be particularly devastating (e.g., open heart surgery and prosthetic arthroplasty), the prophylactic administration of cefoperazone may be continued for 72 hours following the completion of surgery.

4.3 Contraindications

Cefoperazone is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated severe hypersensitivity to beta-lactams (see section 4.4 Special warnings and precautions for use).

4.4 Special warnings and precautions for use

Hypersensitivity

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactam or cephalosporin, including cefoperazone. These reactions are more apt to occur in individuals with a history of hypersensitivity reactions to multiple allergens.

Before therapy with cefoperazone is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs (see section 4.3 Contraindications).[7] Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs.

If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

Severe and occasionally fatal skin reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and dermatitis exfoliative have been reported in patients on cefoperazone therapy. If a severe skin reaction occurs cefoperazone should be discontinued and appropriate therapy should be initiated (see section 4.8 Undesirable effects).

Use in Hepatic Dysfunction

Cefoperazone is extensively excreted in bile. The serum half-life of cefoperazone is usually prolonged and urinary excretion of the drug increased in patients with hepatic diseases and/or biliary obstruction. Even with severe hepatic dysfunction, therapeutic concentrations of cefoperazone are obtained in bile and only a 2 to 4 fold increase in half-life is seen. (see section 4.2 Posology and method of administration).

General

Serious haemorrhage cases, including fatalities, have been reported with cefoperazone as with other antibiotics, vitamin K deficiency resulting in coagulopathy has occurred in patients treated with cefoperazone. The mechanism may possibly be related to the suppression of gut flora which normally synthesize this vitamin. Those at risk include patients with poor diet, malabsorption states (e.g., cystic fibrosis) and patients on prolonged intravenous alimentation regimens. Prothrombin time should be monitored in these patients and patients receiving anticoagulant therapy and exogenous vitamin K administered as indicated. Discontinue cefoperazone if there is persistent bleeding and no alternative explanations are identified.

As with other antibiotics, overgrowth of non-susceptible organisms may occur during prolonged use of cefoperazone. Patients should be observed carefully during treatment. As with any potent systemic agent, it is advisable to check periodically for organ system dysfunction during extended therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in neonates, especially when premature, and other infants.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cefoperazone, 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 antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two

months after the administration of antibacterial agents.

Usage in Infancy

Cefoperazone has been effectively used in infants. It has not been extensively studied in premature infants and neonates. Therefore, in treating premature infants and neonates, potential benefits and possible risks involved should be considered before instituting therapy (see section 6.1 Animal toxicology or pharmacology).

In neonates with kernicterus, cefoperazone does not displace bilirubin from plasma protein binding sites.

4.5 Drug interactions

Alcohol

A disulfiram-like reaction characterized by flushing, sweating, headache and tachycardia has been reported when alcohol was ingested during and as late as the fifth day after the administration of cefoperazone. A similar reaction has been reported with certain other cephalosporins and patients should be cautioned concerning ingestion of alcoholic beverages in conjunction with administration of cefoperazone. For patients requiring artificial feeding orally or parenterally, solutions containing ethanol should be avoided.

Drug Laboratory Test Interactions

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution.

4.6 Use in special populations

Usage During Pregnancy

Reproduction studies have been performed in mice, rats and monkeys at doses up to 10 times the human dose and have revealed no evidence of impaired fertility and did not show any teratological findings. There are, however, 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.

Usage in Nursing Mothers

Only small quantities of cefoperazone are excreted in human milk. Although cefoperazone passes poorly into breast milk of nursing mothers, caution should be exercised when cefoperazone is administered to a nursing mother.

4.7 Effects on ability to drive and use machines

Clinical experience with cefoperazone indicates that it is unlikely to impair a patient's ability to drive or use machinery.

4.8 Undesirable effects

Adverse Reactions Table

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Coagulopathy*, Hypoprothrombinaemia, Neutropenia, Coombs direct test positive, Haemoglobin decreased, Haematocrit decreased, Thrombocytopenia*, Eosinophilia
Immune system disorders	Anaphylactic shock*, Anaphylactic reaction*, Anaphylactoid reaction (including shock)*, Kounis syndrome*†, Hypersensitivity*
Vascular disorders	Haemorrhage*, Infusion site phlebitis
Gastrointestinal disorders	Pseudomembranous colitis*, Diarrhoea, Vomiting*
Hepatobiliary disorders	Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood alkaline phosphatase increased, Jaundice*
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis*, Stevens Johnson Syndrome*, Dermatitis exfoliative*, Pruritus*, Urticaria, Rash maculopapular
General disorders and administration site conditions	Administration site pain, Pyrexia

*ADR identified post-marketing.

†Acute coronary syndrome associated with an allergic reaction.

4.9 Overdose

Limited information is available on the acute toxicity of cefoperazone sodium. Overdosage of the drug would be expected to produce manifestations that are principally extensions of the adverse reactions reported with the drug. The fact that high CSF (cerebrospinal fluid) concentrations of β-lactam antibiotics may cause neurologic effects and the potential for seizures should be considered. Since cefoperazone is removed from the circulation by haemodialysis, this procedure may enhance the elimination of the drug from the body should overdosage occur in some patients with impaired renal function

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Cefoperazone, a third-generation cephalosporin, interferes with cell wall synthesis by binding to the penicillin-binding proteins (PBPs), thus preventing cross-linking of nascent peptidoglycan.

5.2. Pharmacodynamic properties

The bactericidal action of cefoperazone results from the inhibition of bacterial cell wall synthesis.

Cefoperazone is active *in vitro* against a wide variety of clinically significant organisms, and is resistant to degradation by many β-lactamases. Susceptible organisms include:

Gram-positive Organisms:

Staphylococcus aureus, penicillinase and non-penicillinase-producing strains
Staphylococcus epidermidis
Streptococcus pneumoniae (formerly *Diplococcus pneumoniae*)
Streptococcus pyogenes (Group A *β-hemolytic streptococci*)
Streptococcus agalactiae (Group B *β-hemolytic streptococci*)
Streptococcus faecalis (*enterococcus*)
β-hemolytic streptococci

Gram-negative Organisms:

Escherichia coli
Klebsiella species
Enterobacter species
Citrobacter species
Haemophilus influenzae
Proteus mirabilis
Proteus vulgaris
Morganella morganii (formerly *Proteus morganii*)
Providencia rettgeri (formerly *Proteus rettgeri*)
Providencia species
Serratia species (including *S. marcescens*)
Salmonella and *Shigella* species
Pseudomonas aeruginosa and some other *Pseudomonas*
Some strains of *Acinetobacter calcoaceticus*

Neisseria gonorrhoeae
Neisseria meningitidis
Bordetella pertussis
Yersinia enterocolitica

Anaerobic Organisms:

Gram-positive and Gram negative cocci (including *Peptococcus, Peptostreptococcus* and *Veillonella* species)

Gram-positive bacilli (including *Clostridium, Eubacterium* and *Lactobacillus* species)

Gram-negative bacilli (including *Fusobacterium* species, many strains of *Bacteroides fragilis* and other species of *Bacteroides*)

5.3 Pharmacokinetic Properties

High serum, bile and urine levels of cefoperazone are attained after a single dose of the drug. Table 1 demonstrates the serum concentrations of cefoperazone in normal volunteers following either a single 15-minute constant rate intravenous infusion of 1, 2, 3 or 4 grams of the drug, or a single intramuscular injection of 1 or 2 grams of the drug. Probenecid has no effect on serum concentrations of cefoperazone.

TABLE 1. CEFOPERAZONE SERUM CONCENTRATIONS

Dose/Route	Mean Serum Concentrations (mcg/ml)						
	0*	0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr
1 g IV	153	114	73	38	16	4	0.5
2 g IV	252	153	114	70	32	8	2
3 g IV	340	210	142	89	41	9	2
4 g IV	506	325	251	161	71	19	6
1 g IM	32**	52	65	57	33	7	1
2 g IM	40**	69	93	97	58	14	4

* Hours post-administration, with 0 time being the end of the infusion.
** Values obtained 15 minutes post-injection.

The mean serum half-life of cefoperazone is approximately 2 hours, independent of the route of administration.

Cefoperazone reaches therapeutic levels in all body fluids and tissues tested. Among these are ascitic and cerebrospinal (in patients with inflamed meninges) fluids; urine; bile and

gallbladder wall; sputum and lung; palatine tonsil and sinus mucous membrane; atrial appendage; kidney, ureter, prostate and testis; uterus and fallopian tube; bone; and umbilical cord blood and amniotic fluid.

Cefoperazone is excreted in both the bile and urine. Maximum bile concentrations are generally obtained between one and three hours following drug administration and exceed concurrent serum concentrations by up to 100 times. Reported biliary concentrations of cefoperazone range from 66 mcg/ml at 30 minutes to as high as 6000 mcg/ml at 3 hours after an intravenous bolus injection of 2 grams in patients without biliary tract obstruction.

After a variety of dosages and routes of administration, the urinary recovery of cefoperazone averages 20% to 30% over a 12-hour period in individuals with normal renal function. Urinary concentrations greater than 2200 mcg/ml have been obtained following a 15-minute infusion of a 2 gram dose. After an IM injection of 2 gram, peak urine concentrations of approximately 1000 mcg/ml have been obtained.

Repeated administration of cefoperazone has not resulted in accumulation of the drug in normal subjects.

Use in Hepatic Dysfunction

In patients with hepatic dysfunction, the serum half-life is prolonged and urinary excretion is increased. In patients with both renal and hepatic insufficiencies, cefoperazone may accumulate in the serum.

Use in Renal Dysfunction

Peak serum concentrations, AUCs, and serum half-lives are similar in normal subjects and in patients with renal insufficiency.

6. NONCLINICAL PROPERTIES

6.1 Animal toxicology or pharmacology

Cefoperazone had adverse effects on the testes of pre-pubertal rats at all doses tested. Subcutaneous administration of 1000 mg per kg per day (approximately 16 times the average adult human dose) resulted in reduced testicular weight, arrested spermatogenesis, reduced germinal cell population and vacuolation of Sertoli cell cytoplasm. The severity of lesions was dose dependent in the 100 to 1000 mg/kg per day range; the low dose caused a minor decrease in spermatocytes. This effect has not been observed in adult rats. Histologically the lesions were reversible at all but the highest dosage levels. However, these studies did not evaluate subsequent development of reproductive function in the rats. The relationship of these findings to humans is unknown.

7. DESCRIPTION

Magnamycin 250 mg:
A flint glass vial of 10 ml capacity containing white or almost white powder free from foreign matter.

Magnamycin 1 g:
A flint glass vial of 20 ml capacity containing white or almost white powder free from foreign matter.

Magnamycin 2 g:
A flint glass vial of 30 ml capacity containing white or almost white powder free from foreign matter.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Aminoglycosides

Solutions of cefoperazone and aminoglycoside should not be directly mixed since there is a physical incompatibility between them. If combination therapy with cefoperazone and an aminoglycoside is contemplated (see section 4.1 Therapeutic indications) this can be accomplished by sequential intermittent intravenous infusion provided that separate secondary intravenous tubing is used, and that the primary intravenous tubing is adequately irrigated with an approved diluent between doses. It is also suggested that cefoperazone be administered prior to the aminoglycoside.

8.2 Shelf-life

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The following parenteral diluents and approximate concentrations of cefoperazone provide stable solutions under the following conditions for the indicated time periods. Controlled room temperature of (15°C-25°C) for 24 hours (After the indicated time periods, unused portions of solutions should be discarded).

Solutions	Approximate Concentrations
5% Dextrose Injection	2 mg to 50 mg/ml
5% Dextrose and Lactated Ringer's Injection	2 mg to 50 mg/ml
5% Dextrose and 0.9% Sodium Chloride Injection	2 mg to 50 mg/ml
5% Dextrose and 0.2% Sodium Chloride Injection	2 mg to 50 mg/ml
10% Dextrose Injection	2 mg to 50 mg/ml
Lactated Ringer's Injection	2 mg/ml
0.5% Lidocaine Hydrochloride Injection	300 mg/ml
0.9% Sodium Chloride Injection	2 mg to 300 mg/ml
Sterile Water for Injection	300 mg/ml

Reconstituted cefoperazone solutions may be stored in glass or plastic syringes, or in glass or flexible plastic parenteral solution containers for 5 days at refrigerator temperatures of (2°- 8°C).

Solutions	Approximate Concentrations
5% Dextrose Injection	2 mg to 50 mg/ml
5% Dextrose and 0.9% Sodium Chloride Injection	2 mg to 50 mg/ml
5% Dextrose and 0.2% Sodium Chloride Injection	2 mg to 50 mg/ml
Lactated Ringer's Injection	2 mg/ml
0.5% Lidocaine Hydrochloride Injection	300 mg/ml
0.9% Sodium Chloride Injection	2 mg to 300 mg/ml
Sterile Water for Injection	300 mg/ml

Reconstituted cefoperazone solutions may be stored in glass or plastic syringes, or in glass or flexible plastic parenteral solution containers for 3 weeks at freezer temperatures of (–20° to -10°C).

Solutions	Approximate Concentrations
5% Dextrose Injection	50 mg/ml
5% Dextrose and 0.9% Sodium Chloride Injection	2 mg/ml
5% Dextrose and 0.2% Sodium Chloride Injection	2 mg/ml
5 Weeks	
0.9% Sodium Chloride Injection	300 mg/ml
Sterile Water for Injection	300 mg/ml

Reconstituted cefoperazone solutions may be stored in plastic syringes, or in flexible plastic parenteral solution containers.

Frozen samples should be thawed at room temperature before use. After thawing, unused portions should be discarded. Do not refreeze.

8.3 Packaging information

Clear glass vial stoppered with rubber plug and fitted with flip off seal.

Available as 250 mg, 1 g and 2 g packs.

8.4 Storage and handling instructions

Till reconstitution, store below 25°C. Protect from light.

Handling instructions

Intravenous Administration

Vials of Cefoperazone sterile powder may be initially reconstituted with a minimum of 2.8 ml per gram of cefoperazone of any compatible reconstituting solution appropriate for intravenous administration listed below in Table 2. For ease of reconstitution, the use of 5 ml compatible solution per gram of cefoperazone is recommended.

Table 2. Solutions for Initial Reconstitution

5% Dextrose Injection
10% Dextrose Injection
5% Dextrose and 0.9% Sodium Chloride Injection
0.9% Sodium Chloride Injection
5% Dextrose and 0.2% Sodium Chloride Injection
Sterile Water for Injection

The entire quantity of the resulting solution should then be further diluted for administration using any of the following vehicles for intravenous infusion listed below in Table 3:

Table 3. Vehicles for Intravenous Infusion

5% Dextrose Injection
10% Dextrose Injection
5% Dextrose and Lactated Ringer's Injection
Lactated Ringer's Injection
0.9% Sodium Chloride Injection
5% Dextrose and 0.9% Sodium Chloride Injection
5% Dextrose and 0.2% Sodium Chloride Injection

Intramuscular Administration

Sterile Water for Injection may be used to prepare cefoperazone for intramuscular injection. When concentrations of 250 mg/ml or more are to be administered, a Lidocaine solution should be used. These solutions should be prepared using a combination of Sterile Water for Injection and 2% Lidocaine Hydrochloride Injection that approximates a 0.5% Lidocaine Hydrochloride Solution. A two-step dilution process as follows is recommended: First, add the required amount of Sterile Water for Injection and agitate until cefoperazone powder is completely dissolved. Second, add the required amount of 2% Lidocaine and mix.

Vial	**Final Cefoperazone concentration**	**Step 1 Volume of Sterile Water**	**Step 2 Volume of 2% Lidocaine**	**Withdrawable Volume†**
250 mg vial	250 mg/ml 333 mg/ml	0.7 ml 0.4 ml	0.2 ml 0.2 ml	1.0 ml 0.75 ml
1.0 g vial	250 mg/ml 333 mg/ml	2.6 ml 1.8 ml	0.9 ml 0.6 ml	4.00 ml 3.00 ml
2.0 g vial	250 mg/ml 333 mg/ml	5.2 ml 3.7 ml	1.8 ml 1.2 ml	8.00 ml 6.00 ml

† There is sufficient excess present to allow for withdrawal and administration of the stated volumes.

9. PATIENT COUNSELLING INFORMATION

Patients should be counseled that antibacterial drugs including MAGNAMYCIN should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When MAGNAMYCIN is prescribed to treat a bacterial infection,

patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treated by MAGNAMYCIN or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibacterial drugs which usually ends when the drug is discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible.

10. DETAILS OF MANUFACTURER

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11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Refer to outer carton.

12. DATE OF REVISION

July 2023