PRODUCT INFORMATION

KEFLIN®

CEFALOTIN SODIUM FOR INJECTION
NEUTRAL

DESCRIPTION

KEFLIN (cefalotin sodium), Neutral, is a semisynthetic cephalosporin antibiotic for parenteral use. It is the sodium salt of 7-(thiophene-2-acetamido) cephalosporanic acid. Sodium bicarbonate has been added to result in reconstituted solutions having a pH ranging between 6 and 8.5. The total sodium content is approximately 63 mg (2.8 mEq. sodium ion) per g of KEFLIN Neutral.

MICROBIOLOGY/PHARMACOLOGY

Microbiology - The in-vitro bactericidal action of cefalotin results from inhibition of cell-wall synthesis. In general, cefalotin has higher activity against Gram positive than Gram negative organisms, the latter varying greatly in their sensitivity to the drug. The range of antibiotic concentrations at which bacteria are inhibited may vary substantially according to the isolate, therefore susceptibility testing is highly desirable. KEFLIN is usually active against the following organisms in-vitro:

- Beta-haemolytic and other streptococci (most strains of enterococci, e.g. *Streptococcus faecalis* are resistant).
- Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains. Methicillin-resistant staphylococci are resistant.
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Escherichia coli*
- *Klebsiella*
- *Proteus mirabilis*

NOTE: *Pseudomonas* organisms are resistant to KEFLIN, as are most indole-producing *Proteus* species and motile *Enterobacter* species.

Susceptibility Plate Tests - If the Bauer-Kirby-Sherris-Turck method of disc susceptibility testing is used, a disc containing 30 mcg cefalotin should give a zone of over 17 mm when tested against a cefalotin-susceptible bacterial strain, and a zone of over 14 mm with an organism of intermediate susceptibility.
Human Pharmacology - KEFLIN is not absorbed significantly following oral administration. It is intended for parenteral administration only. After administration of a 500 mg dose intramuscularly to normal volunteers, the average peak serum antibiotic level was 10 mcg per mL at one-half hour; with a 1 g dose, the average was about 20 mcg per mL. Following a single 1 g intravenous dose of KEFLIN, blood levels have been about 30 mcg per mL at fifteen minutes, have ranged from 3 to 12 mcg at one hour, and have declined to about 1 mcg at four hours. With continuous infusion, at the rate of 500 mg per hour, levels have been from 14 to 20 mcg per mL of serum.

Dosages of 2 g given intravenously over a thirty-minute period have produced serum concentrations of 80 to 100 mcg per mL one-half hour after the infusion; levels ranged from 10 to 40 mcg per mL at one hour and from 3 to 6 mcg per mL at two hours and were not assayable after five hours. Cefalotin has a serum half life of approximately fifty minutes in subjects with normal renal function. This may be prolonged considerably in patients with impaired renal function.

Sixty to seventy percent of an intramuscular dose is excreted by the kidneys in the first six hours; this results in high urine levels, e.g. 800 mcg per mL of urine after a 500 mg dose and 2500 mcg per mL following 1 g. Probenecid slows tubular excretion and almost doubles peak blood levels. Approximately 30% of the administered dose is excreted as the O-desacetyl metabolite. Cerebrospinal fluid levels of KEFLIN are low and unpredictable. The antibiotic passes readily into other body fluids, e.g. pleural, joint, and ascitic fluids. Studies of amniotic fluid and cord blood show prompt transfer of KEFLIN across the placenta. Secondary aqueous-humour levels have averaged 0.5 mcg per mL thirty minutes after a single 1 g intravenous dose. The antibiotic has been detected in bile.

INDICATIONS

KEFLIN is indicated in the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below. Culture and susceptibility studies should be performed. Therapy may be instituted before results of susceptibility studies are obtained (See notes under Microbiology).

Respiratory tract infections caused by S. pneumoniae, staphylococci (penicillinase and non-penicillinase-producing), group A beta-haemolytic streptococci, Klebsiella, and H. influenzae.

Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and non-penicillinase-producing), group A beta-haemolytic streptococci, E. coli, Pr. mirabilis, and Klebsiella.

Genito-urinary tract infections caused by E. coli, Pr. mirabilis and Klebsiella.

Septicaemia, including endocarditis, caused by S. pneumoniae, staphylococci (penicillinase and non-penicillinase-producing), group A beta-haemolytic streptococci, S. viridans; E. coli, Pr. mirabilis, and Klebsiella.
Bone and joint infections caused by staphylococci (penicillinase and non-penicillinase-producing).

Prophylactically in vaginal hysterectomy, head and neck surgery, insertion of prosthetic heart valves, and prosthetic arthroplasty. Cefalotin is not recommended for G.I. procedures or other sites where anaerobic organisms such as bacteroides tend to prevail. Dosage is required pre-, intra- and post-operatively (i.e. perioperatively - See DOSAGE and ADMINISTRATION).

If signs of postoperative infection develop, specimens should be cultured to identify the causative organism so that appropriate therapy can be instituted.

NOTE: If the susceptibility tests show that the causative organism is resistant to KEFLIN, other appropriate antibiotic therapy should be instituted.

CONTRAINDICATION

KEFLIN is contraindicated in persons who have shown hypersensitivity to the cephalosporin group of antibiotics or who have previously experienced a major allergy to penicillin (see WARNINGS).

WARNINGS

Before cefalotin therapy is instituted, careful inquiry should be made concerning previous hypersensitivity reactions to cephalosporins and penicillin. Cephalosporin C derivatives should be given cautiously in penicillin-sensitive patients.

Serious acute hypersensitivity reactions may require adrenaline and other emergency measures.

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. Before initiating therapy with KEFLIN, careful enquiry should be made concerning previous hypersensitivity reactions to ß-lactam antibiotics.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exception should be made with regard to KEFLIN.
Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including KEFLIN. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider the diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

**Use in Pregnancy** - Pregnancy Category A

**Use in Lactation** - The safety of cefalotin in the nursing human newborn has not been established.

Cefalotin is excreted in breast milk and therefore it is not advised for administration to nursing mothers unless alternative arrangements for feeding the infant can be made.

**PRECAUTIONS**

Patients should be followed carefully so that any side-effects or unusual manifestations of drug idiosyncrasy may be detected.

If an allergic reaction to KEFLIN occurs, the drug should be discontinued and the patient treated with the usual agents (e.g. adrenaline, or other pressor amines, antihistamines or corticosteroids).

Although KEFLIN 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 DOSAGE and ADMINISTRATION. Usual doses in such individuals may result in excessive serum concentrations.

When intravenous doses of KEFLIN larger than 6 g daily are given by infusion for periods longer than three days, they may be associated with thrombophlebitis, and the veins may have to be alternated. The addition of 10 to 25 mg of hydrocortisone to intravenous solutions containing 4 to 6 g of cefalotin may reduce the incidence of thrombophlebitis. The use of small I.V. needles in the larger available veins may be preferred.

Prolonged use of KEFLIN 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.
A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with Clinitest tablets but not with Tes-Tape (urine sugar analysis paper, Lilly).

An increased incidence of nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Because antibiotics may alter intestinal flora and/or have adverse effects on the gastrointestinal system, caution should be exercised when prescribing antibiotics to individuals with a history of gastrointestinal disease, particularly colitis.

**ADVERSE REACTIONS**

**Hypersensitivity** - Maculopapular rash, urticaria, reactions resembling serum sickness, and anaphylaxis have been reported.

There has been one report that administration of high doses of cefalotin by rapid intravenous infusion for a prolonged period has been associated with a serum sickness type of reaction. No similar findings have since been reported. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

**Blood** - Several instances of neutropenia in patients receiving KEFLIN have been reported. Though the patients had received several other medications and had shown allergy to other antibiotics, the return of the low white-cell count and neutropenia to normal after KEFLIN was discontinued suggested a causal relationship. It is therefore advisable that patients receiving KEFLIN treatment for one week or more should have a white blood cell count.

Some individuals, particularly those with azotaemia, have developed positive direct Coombs' tests during cefalotin therapy. Thrombocytopenia and haemolytic anaemia have been reported.

**Gastrointestinal** - As with some other antibiotics, colitis, including rare instances of pseudomembranous colitis, has been reported in conjunction with therapy with KEFLIN. Nausea and vomiting have been reported rarely.

**Liver** - Transient rise in AST and alkaline phosphatase has been noted.

**Kidney** - Rise in BUN and decreased creatinine clearance have been reported, particularly in patients with prior renal impairment. The role of KEFLIN in renal changes is difficult to assess, because other factors predisposing to prerenal azotaemia or to acute renal failure usually have been present.
Local Reactions - Pain, induration, tenderness, and elevation of temperature have been reported following repeated intramuscular injections. Thrombophlebitis has occurred and is usually associated with daily doses of over 6 g given by infusion for more than three days.

DOSAGE AND ADMINISTRATION

In adults, the usual dosage range is 500 mg to 1 g of cefalotin every four to six hours. A dosage of 500 mg every six hours is adequate in uncomplicated pneumonia, furunculosis with cellulitis, and most urinary tract infections.

In severe infections, this may be increased by giving the injections every four hours or, when the desired response is not obtained, by raising the dose to 1 g. In life-threatening infections, in patients with normal renal function, doses up to 2 g every four hours may be required.

For perioperative prophylactic use to prevent postoperative infection in vaginal hysterectomy, head and neck surgery, insertion of prosthetic heart valves, and prosthetic arthroplasty in adults, the following doses are recommended:

(a) 2 g administered I.V. just prior to surgery (approximately one-half to one hour before the initial incision);

(b) 2 g during surgery (administration modified according to the duration of the operative procedure); and

(c) 2g q.6h. postoperatively for 24 hours. In heart valve replacement and arthroplasty it is recommended that KEFLIN should be continued for 72 hours.

In children, 20 to 30 mg per kg may be given at the times designated above.

Since cefalotin has a serum half-life of 30 to 50 minutes, it is important that (1) the preoperative dose be given just prior to the start of surgery so that adequate antibiotic levels are present in the serum and tissues at the time of initial surgical incision; and (2) KEFLIN be administered (only if necessary) at appropriate intervals during surgery to provide sufficient levels of the antibiotic at the anticipated moments of greatest exposure to infective organisms.

When renal function is reduced, an intravenous loading dose of 1 to 2 g may be given. Continued dosage schedule should be determined by degree of renal impairment, severity of infection and susceptibility of the causative organism. The maximum doses administered should be based on the following recommendations.
DOSAGE OF KEFLIN WHEN RENAL FUNCTION IS IMPAIRED.

<table>
<thead>
<tr>
<th>STATUS OF RENAL FUNCTION</th>
<th>MAXIMUM ADULT DOSAGE (Maintenance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Impairment (C(_r)=80-50 mL/min)</td>
<td>2 g q. 6 h.</td>
</tr>
<tr>
<td>Moderate Impairment (C(_r)=50-25 mL/min)</td>
<td>1.5 g q. 6 h.</td>
</tr>
<tr>
<td>Severe Impairment (C(_r)=25-10 mL/min)</td>
<td>1 g q. 6 h.</td>
</tr>
<tr>
<td>Marked Impairment (C(_r)=10-2 mL/min)</td>
<td>0.5 g q. 6 h.</td>
</tr>
<tr>
<td>Essentially No Function (C(_r)= 2 mL/min)</td>
<td>0.5 g q. 8 h.</td>
</tr>
</tbody>
</table>

In infants and children, the dosage should be proportionately less in accordance with age, weight, and severity of the infection.

In infants below 2 kg weight, a dose of 20 mg/kg every 12 hours is recommended. In older children, daily administration of 100 mg per kg (80 to 160 mg per kg) in divided doses has been found effective for most infections susceptible to KEFLIN.

Antibiotic therapy in beta-haemolytic streptococcal infections should continue for at least ten days. In staphylococcal infections, surgical procedures, such as incision and drainage, should be carried out in all cases when indicated.

KEFLIN may be given intravenously or by deep intramuscular injection into a large muscle mass, such as the gluteus or lateral aspect of the thigh, to minimise pain and induration.

**Intramuscular** - Each gram of cefalotin should be diluted with 4 mL of Sterile Water for Injection.

The reconstituted material will provide two 500 mg doses of approximately 2.5 mL each. If the vial contents do not completely dissolve, an additional small amount of diluent (e.g. 0.2 to 0.4 mL) may be added and the contents warmed slightly.

**Intravenous** - The intravenous route may be preferable for patients with bacteraemia, septicaemia, or other severe or life-threatening infections who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending. For these infections, in patients with normal renal function, the intravenous dosage is 4 to 12 g of cefalotin daily. Then, depending on the clinical response and laboratory findings, the dosage may gradually be reduced.
For intermittent intravenous administration, a solution containing 1 g KEFLIN in 10 mL of diluent may be slowly injected directly into the vein over a period of three to five minutes or may be given through the tubing when the patient is receiving one of the following parenteral solutions:

- 5% Glucose Injection
- 0.9% Sodium Chloride Injection
- Lactated Ringer's Injection, USP
- Glucose 5% in Lactated Ringer's Injection

Intermittent intravenous infusion with Y-type administration set can also be accomplished while bulk intravenous solutions are being infused. However, during infusion of the solution containing KEFLIN, 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 KEFLIN so that the calculated dose will be infused.

When a Y-tube hookup is used, the contents of the 1 g vial of cefalotin should be diluted by addition of 10 mL Sterile Water for Injection, 5 percent Glucose Injection, or 0.9 percent Sodium Chloride Injection.

For continuous intravenous infusion, 4 g of cefalotin, diluted and well mixed with at least 20 mL of Sterile Water for Injection, may be added to an I.V. bottle containing 5 percent glucose solution, normal saline solution, Lactated Ringer's Injection, USP, Glucose 5% in Lactated Ringer's Injection. The choice of saline or glucose solution and the volume to be employed is dictated by fluid and electrolyte management.

Intraperitoneal - In peritoneal dialysis procedures, cefalotin has been added to dialysis fluid in concentrations up to 6 mg per 100 mL and instilled into the peritoneal space throughout an entire dialysis (sixteen to thirty hours). Assay procedures have shown that 44 percent of the administered drug was absorbed into the bloodstream. Serum levels of 10 mcg per mL were reported, with no evidence of accumulation and no untoward local or systemic reactions.

The intraperitoneal administration of solutions containing 0.1 to 4 percent KEFLIN in saline has been used in treating patients with peritonitis or contaminated peritoneal cavities. (The total daily dosage of KEFLIN should take into account the amount given by the intraperitoneal route).

**STABILITY**

While stored under refrigeration, the solution has a satisfactory potency for forty-eight hours after reconstitution.

Solutions may precipitate; they can be redissolved by being warmed to room temperature with constant agitation. Kept at room temperature, solutions for intramuscular injection should be given within six hours after being mixed.
Intravenous infusions should be started within six hours and completed within twenty-four hours. For prolonged infusions, replace with a freshly prepared solution at least every twenty-four hours.

The concentrated solution will darken, especially at room temperature. Slight discolouration of the solution is permissible.

Solutions of KEFLIN Neutral in Sterile Water for Injection that are frozen immediately after reconstitution in the original container are stable for as long as six weeks when stored at -20°C. If the product is warmed, care should be taken to avoid heating after the thawing is complete. Once thawed, solutions should not be refrozen and should be used within the time periods mentioned above. Any unused solution should be discarded.

**OVERDOSAGE**

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 DOSAGE and ADMINISTRATION). If seizures occur, the drug should be promptly discontinued; anticonvulsant therapy may be administered if clinically indicated. Haemodialysis may be considered in cases of overwhelming overdosage. A maintenance dose of KEFLIN should be administered following haemodialysis; however, there is an absence of data from well-controlled studies to make more specific recommendations.

**HOW SUPPLIED**

KEFLIN Neutral, equivalent to 1 g cefalotin, in 10 mL size rubber-stoppered vials.

**SPONSOR**

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