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Pneumonia is the leading cause of infectious death among debilitated patients. Your choice of antibiotic is crucial to their care. For over 16 million patient-days of therapy, CEFOBID (cefoperazone sodium) has offered an excellent therapeutic profile:

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• No dosage adjustment needed for the renally or hepatically impaired

• Contraindicated in patients with known allergy to the cephalosporin class of antibiotics

CEFOBID (cefoperazone sodium)

IM/IV
q12h
1g and 2g vials

1 Due to susceptible strains of indicated organisms, including Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, and Enterobacter species.

2 Cefazolin/gentamicin or ceftriaxone/gentamicin

3 Rocephin (ceftriaxone sodium) is a registered trademark of Roche Laboratories.

Please see adjacent page for brief summary of CEFOBID (cefoperazone sodium) prescribing information.
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Editor: Josephine A. Morello

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Full-course antibiotic therapy in half the usual time

NEW  ONCE DAILY FOR 5 DAYS  
Zithromax (AZITHROMYCIN) 250-mg capsules

©1992, Pfizer Inc

Please see brief summary of prescribing information on last page of this advertisement.
Zithromax™ (azithromycin) is targeted to sites of bacterial infection. Zithromax penetrates and concentrates in infected tissue.¹-⁴

In three animal models, Zithromax demonstrated higher concentrations in infected tissues.

Zithromax concentrations were measured in infected and noninfected tissues. (Data on file.)

Concentrations in animal tissues do not relate directly to concentrations in humans. Tissue concentrations may not be quantitatively related to efficacy; however, Zithromax’s extensive tissue distribution may be relevant to clinical activity.
Zithromax concentrations in human tonsillar tissue following 1-day dosing.
(Adapted from Foulds et al.)

Projected tissue and serum levels of 5-day dosing

Projected tissue and serum concentrations were generated using pharmacokinetic modeling. The observed tissue levels from 1-day dosing were used in the model to project tissue concentrations for 5-day dosing.
(Data on file.)

NEW ONCE DAILY FOR 5 DAYS Zithromax™ (AZITHROMYCIN) 250-mg capsules

Please see brief summary of prescribing information on last page of this advertisement.
**NEW PROVIDES.**

The efficacy you want — with once-daily dosing, for just 5 days

<table>
<thead>
<tr>
<th>Acute bacterial exacerbations of COPD (chronic bronchitis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zithromax™ (azithromycin)</strong></td>
</tr>
<tr>
<td>5 days/5 doses</td>
</tr>
<tr>
<td><strong>Clinical response (%)</strong></td>
</tr>
<tr>
<td>100%</td>
</tr>
<tr>
<td>CURED 33%</td>
</tr>
<tr>
<td>IMPROVED 67%</td>
</tr>
</tbody>
</table>

In a multicenter, randomized, comparative trial, patients with acute bacterial exacerbations of chronic bronchitis received either the standard dose of Zithromax or cefaclor, 500 mg bid for 10 days. Efficacy was based on percentages of clinical response and bacterial eradication at day 11 of follow-up. (Adapted from Dark; Data on file.)

* Clinical response at the end of therapy was defined as: cured, based upon complete resolution of signs and symptoms; improved, based upon improvement but not complete resolution of signs and symptoms; or failed, based upon no improvement in signs and symptoms.

**Zithromax** is indicated for patients 16 years of age and older with mild to moderate infections, such as:

- Acute bacterial exacerbations of COPD (chronic bronchitis) due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *S pneumoniae*
- Community-acquired, outpatient pneumonia due to *S pneumoniae* or *H influenzae*

Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with nosocomially-acquired infections; patients with known or suspected bacteremia; patients requiring hospitalization; elderly or debilitated patients; or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia)

- Streptococcal pharyngitis and tonsillitis due to *S pyogenes* as an alternative to first-line therapy with penicillin in patients who cannot use first-line therapy
- Uncomplicated skin infections due to *S aureus*, *S pyogenes*, or *Streptococcus agalactiae*
- Nongonococcal urethritis and cervicitis due to *Chlamydia trachomatis*
Improved potential for patient compliance with convenient dosing

### In respiratory tract and skin infections

<table>
<thead>
<tr>
<th>Zithromax (qd x 5 days)</th>
<th>VS</th>
<th>amoxicillin/clavulanate (tid x 10 days)</th>
<th>30 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 doses</td>
<td></td>
<td>cefaclor (tid x 10 days)</td>
<td>30 doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ciprofloxacin (bid x 7–14 days)</td>
<td>14-28 doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin (bid x 7–14 days)</td>
<td>14-28 doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>erythromycin (bid-qid x 10 days)</td>
<td>20-40 doses</td>
</tr>
</tbody>
</table>

### In urethritis and cervicitis

<table>
<thead>
<tr>
<th>Zithromax (a single 1-g dose)</th>
<th>VS</th>
<th>doxycycline (bid x 7 days)</th>
<th>14 doses</th>
</tr>
</thead>
</table>

- A favorable safety profile with a low (0.7%; n=4949) discontinuation rate due to side effects. In multidose trials, the most common side effects were diarrhea/loose stools (5.0%), nausea (3.0%), and abdominal pain (3.0%).

NEW Zithromax™

(AZITHROMYCIN) 250-mg capsules

Please see brief summary of prescribing information on last page of this advertisement.
For respiratory tract and skin infections: 500-mg single dose on day 1; 250 mg once daily on days 2 through 5. Total dose is 1.5 g.

Zithromax should be given either 1 hour before or 2 hours after a meal.
Before you know the sensitivities:

When you have to be right from the start...
Start with Claforan®.
A 10-year record of effective, safe use in empiric therapy* for a wide range of infections
- A 10-year standard for third-generation cephalosporins for efficacy, safety and economy
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- Clinical benefits from office to hospital to outpatient care — from pediatrics to geriatrics

q12h/q8h

Claforan® (cefotaxime sodium)*

A decade of right starts.

* Therapy may be instituted before the results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

1 to 2 g for uncomplicated gram-negative infections
2 g to 4 g for moderate to severe infections
U.S. Patent No. 4,151,439 Claforan® is a trademark of ROUSSEAU-ULFAB.
Please see following page for brief summary of prescribing information.
Brief Summary

INDICATIONS AND USAGE
Treatment
Cloran® is indicated for the treatment of patients with serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below.

1. Acute bacterial sinusitis, including pneumonia, caused by Streptococcus pneumoniae (formerly Diplococcus pneumoniae), Staphylococcus pyogenes (Group A Streptococci) and other streptococci (except enterococci) (See area below), gram-negative bacilli, and haemorrhagic and non-penicillinase producing, Escherichia coli, Klebsiella species, Haemophilus influenzae (including ampicillin-resistant strains), Haemophila parainfluenzae, Proteus mirabilis, Serratia marcescens, Enterobacter species, indole-positive and Proteus species (including P. mirabilis).

2. Genitourinary infections. Urinary tract infections caused by Enterococcus species, Staphylococcus epidermidis, Staphylococcus aureus (penicillinase and non-penicillinase producing), Citrobacter species, Enterobacter species, Klebsiella species, Proteus mirabilis, Proteus vulgaris, Proteus incondens G. Morganii morganii, Providencia rettgeri, Serratia marcescen, and Pseudomonas species. In addition to non-absorbable antibacterial. Also, uncomplicated gonorrhea of multiple or single sites caused by Neisseria gonorrhoeae, including penicillinase producing strains or (See area below).

3. Gynecologic infections, including pelvic inflammatory disease, endometritis and pelvic cellulitis caused by Staphylococcus epidermidis, Staphylococcus species, Enterobacter species, Escherichia coli, Klebsiella species, Proteus mirabilis, Bacteroides species (including Bacteroides fragilis), Clostridium species (including C. perfringens, C. tetani, C. novyi, C. sordellii, and C. septicum), or Fusobacterium species (including F. nucleatum).


5. Skin and skin structure infections caused by Staphylococcus aureus (penicillinase and non-penicillinase producing), Staphylococcus epidermidis (Group A and G. Streptococci), and other streptococci, Enterococcus species, Acinetobacter species, Escherichia coli, Citrobacter species (including C. freundii), Enterobacter species, Klebsiella species, Proteus mirabilis, Proteus vulgaris, Morganella morganii, Providencia rettgeri, Pseudomonas species, Serratia marcescens, Bacteroides species, and anaerobic cocci (including Peptostreptococcus species and Peptococcus species).

6. Intra-abdominal infections, including peritonitis caused by Staphylococcus species, Escherichia coli, Klebsiella species, Bacteroides species, anaerobic cocci (including Peptostreptococcus species and Peptococcus species).

7. Peri-operative or postoperative infections caused by Staphylococcus species, Bacteroides species, anaerobic cocci (including Peptostreptococcus species and Peptococcus species).

8. Central nervous system infections, e.g., meningitis and ventriculitis, caused by Neisseria meningitidis, Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae, and Haemophilus parainfluenzae Escherichia coli, and Pseudomonas aeruginosa.


10. Bacteremia/septicemia caused by Staphylococcus species, Bacteroides species, anaerobic cocci (including Peptostreptococcus species and Peptococcus species), Proteus mirabilis, and Clostridium species.

11. Bacteremia/septicemia caused by Staphylococcus aureus (penicillinase and non-penicillinase producing strains), Streptococcus species (including S. pyogenes), Pseudomonas species (including P. aeruginosa), and Proteus mirabilis.

Although many strains of enterococci (e.g., S. faecalis) and Pseudomonas species are resistant to cephalaxin sodium in vitro, Cloran® has been used successfully in treating patients with infections caused by susceptible organisms.

Specimens for bacteriologic culture should be obtained prior to therapy in order to isolate and identify causative organisms and to determine their susceptibility to Cloran. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

Precautions

- In patients undergoing gastrointestinal, preoperative bowel preparation by mechanical cleansing as well as oral intake of fluids, use cautiously.

- In patients with impaired renal function, use cautiously, dosage adjustment needed.

- In patients with impaired renal function, use cautiously, dosage adjustment needed.

- If symptoms of severe infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapy may be instituted.

CONTRAINDICATIONS

Cloran® is contraindicated in patients who have shown hypersensitivity to cephalaxin sodium or the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CLORAN® IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD先前 HYPERSENSITIVITY REACTIONS TO CEFALEXIN SODIUM, CEPHALOSPORINS, PENCILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN WITH CAUTION TO INDIVIDUALS WITH A HISTORY OF HYPERSENSITIVITY REACTIONS TO PENCILLINS OR OTHER DRUGS. CROSS-SENSITIVITY WITH PENCILLINS AND OTHER POTENTIALLY HYPERSENSITIVITY REACTIONS TO EXTREME URGENCY. USE OF CLORAN® SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO PENCILLINS. IF AN ALLERGIC REACTION OCCURS, DISCONTINUE TREATMENT WITH THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Penicillin-sensitive patients have a high incidence of cephalosporin antibodies (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients with mild manifestations of allergy to penicillin.

TREATMENT with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clindamycin. Studies indicate a toxin produced by Clostridium difficile is one primary cause of antibiotic-associated colitis. Chloramphenicol and ciprofloxacin have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuation alone.

Severe to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuation or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by C. difficile. Other causes of colitis should also be considered.

PRECAUTIONS

Cloran® should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Cloran® has not been shown to be nephrotoxic; however, because high and prolonged serum antibiotic concentrations can occur from usual doses in patients with transient or persistent reduction of urinary output because of renal insufficiency, the total daily dosage should be reduced when Cloran® is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organism.

Although there is no clinical evidence supporting the necessity of changing the dosage of cephalaxin sodium in patients with even profound renal dysfunction, it is suggested that, until further data are obtained, the dose of cephalaxin sodium be halved in patients with estimated creatinine clearances of less than 20 ml/min/1.73 m².

When serum creatinine is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value to creatinine clearance. The serum creatinine value should represent a steady state of renal function.

**Male:**

Weight (kg) × (140 – age) / 72 × serum creatinine

0.85 × above value

For males and other antibiotics, prolonged use of Cloran® may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

As with other beta-lactam antibiotics, granulocytopenia and, more rarely, agranulocytosis may develop during treatment with Cloran®, particularly if given over long periods. For courses of treatment lasting longer than 10 days, blood counts should therefore be monitored.

Drug Interactions: Increased nephrotoxicity has been reported following concomitant administration of cephalaxin and ampicillin and potassium antibiotics.

Contraindications: Long-term studies in animals have not been performed to evaluate carcinogenic potential. Mutagenic tests included a microcomet and an Ames test. Both tests were negative for mutagenicity.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to 30 times the usual human dose and have revealed no evidence of impaired fertility or harm to the fetus because of cephalaxin sodium. However, there are no well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: Use of the drug in women of childbearing potential requires that the anticipated benefit be weighed against the possible risk.

In perfusion and postnatal studies with dogs, the pups in the group given 1200 mg/kg of Cloran® were significantly lighter in weight at birth and remained smaller than pups in the control group during the 21 days of nursing.

Nursing Mothers: Cloran® is excreted in human milk in low concentrations. Caution should be exercised when Cloran® is administered to a nursing woman.

Pediatric Use: Use of the drug for children from birth to 12 years of age is classified as clariotopic, drug can be used during or after antibiotic treatment of critical infections. In infants and young children, Cloran® has been administered IM or IV after reconstitution. Premixed Cloran® Injection is intended for IV administration after thawing. The maximum daily dosage should not exceed 12 1/2 grams every 4 hours IV. For patients with renal impairment, the initial dose of Cloran® may be reduced. The dose may be reduced in patients with impaired renal function. Cloran® should be administered IM or IV after reconstitution. Premixed Cloran® Injection is intended for IV administration after thawing. The maximum daily dosage should not exceed 12 1/2 grams every 4 hours IV. For patients with renal impairment, the initial dose of Cloran® may be reduced. The dose may be reduced in patients with impaired renal function. Cloran® should be administered IM or IV after reconstitutio
PROCRIT®
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Offers the most up-to-date information on PROCRIT therapy as well as complete ordering information.

Please see Brief Summary of Prescribing Information on following page.
PROCRIT®
EPOETIN ALFA
For Injection

Before prescribing, please consult complete prescribing information of which the following is a brief summary.

INDICATIONS AND USAGE

Treatment of Anemia of Chronic Renal Failure Patients

PROCRIT is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis (end-stage renal disease) and patients not on dialysis. PROCRIT should be given to maintain the hematocrit (or other blood cell level as manifested by the hemoglobin or hematocrit determinations) and to decrease the need for transfusions in these patients.

PROCRIT is not indicated for patients who require immediate correction of severe anemia. PROCRIT may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion.

Prior to initiation of therapy, the patient's iron stores, including transferrin saturation and serum ferritin levels, should be determined. Transferin saturation should be less than 50% and serum ferritin at least 100 ng/mL. Blood pressure should be adequately controlled prior to initiation of therapy using a combination of antihypertensive agents to decrease the need for transfusions in these patients. PROCRIT is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron, folate, or vitamin B-12 deficiencies, hemolysis or gastrointestinal bleeding which should be managed appropriately.

PROCRIT, at a dose of 100 U/kg three times per week, is effective in decreasing the transfusion requirements in the red blood cell level of anemic, HIV-infected patients treated with AZT, when the endogenous serum erythropoietin level is ≤ 500 mU/mL and when patients are receiving a dose of AZT ≤ 4200 mg/week.

CONTRAINDICATIONS

PROCRIT is contraindicated in patients with:

1. Uncontrolled hypertension
2. Known hypersensitivity to mammalian cell-derived products
3. Known hypersensitivity to Alum or (Human).

WARNINGS

Chronic Renal Failure Patients

Hypertension: Patients with uncontrolled hypertension should not be treated with PROCRIT; blood pressure should be controlled adequately before initiation of therapy.

Hypersensitivity: During PROCRIT therapy, often during the early phase of treatment when the hematocrit is increasing.

For patients who respond to PROCRIT with a rapid increase in hematocrit (e.g., more than 4 points in any two-week period), the dose of PROCRIT should be reduced because of the possible association of excessive rate of rise of hematocrit with an exacerbation of hypertension.

Seizures: Seizures have occurred in patients with CRF participating in PROCRIT clinical trials.

In patients on dialysis, there was a higher incidence of seizures during the first 90 days of therapy (primarily in approximately 2.5% of patients as compared with later timepoints. Given the potential for an increased risk of seizures during the first 90 days of therapy, blood pressure and the presence of premonitory neurolgic symptoms should be monitored closely. Patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy machinery during this period.

Thrombotic Events: During hemodialysis, patients treated with PROCRIT may require increased anticoagulation with heparin to prevent clotting of the artificial kidney. Clotting of the tunneled venous V-V shunt has occurred at an annualized rate of about 0.25 events per patient-year on PROCRIT therapy overall. For patients with CRF (whether on dialysis or not), other thrombotic events (e.g., myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis) have occurred at an annualized rate of less than 0.04 events per patient-year on PROCRIT therapy. Patients with pre-existing vascular disease should be monitored closely.

In contrast to CRF patients, PROCRIT therapy has not been linked to exacerbation of hypertension, seizures, and thrombotic events in HIV-infected patients.

PRECAUTIONS

Chronic Renal Failure Patients and AZT-treated HIV-Infected Patients

General: The parenteral administration of any biologic product should be attended by appropriate aseptic technique and sterile technique (e.g., needleless systems). Should any reaction occur, the product should be withdrawn immediately. In some cld patients, a transient rash has occurred following PROCRIT therapy, no serious allergic or anaphylactic reactions have been reported.

Hematology: Anemia or pancytopenia may be observed in patients treated with PROCRIT. While neutrophils and platelets may be decreased during the first few weeks of therapy, they usually increase to normal levels over time. Because of the potential for severe neutropenia and thrombocytopenia, patients treated with PROCRIT should have complete blood cell counts obtained weekly during the first 12 weeks of therapy and at least every 4 weeks thereafter. In some patients, a transient rash has occurred following PROCRIT therapy, no serious allergic or anaphylactic reactions have been reported.

Hematology: Exacerbation of porphyria has been observed rarely in PROCRIT-treated patients with CRF. However, PROCRIT has not caused increased urinary excretion of protoporphyrin or coproporphyrin. In some patients with chronic hemolytic anemia, a transient increase in urinary coproporphyrin and protoporphyrin has been observed. In patients with anemia of chronic renal failure, the possibility of protracted anemia or aplastic anemia should be considered.

In some female patients, menses have resumed following PROCRIT therapy; the possibility of potential pregnancy should be discussed and the need for contraception evaluated.

In some clinical studies in dogs and rats, but not in monkeys, PROCRIT therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The daily dose of PROCRIT may result in bone marrow fibrosis in a matched group of patients who had not been treated with PROCRIT.

Hematocrit in CRF patients should be measured twice a week; AZT-treated HIV-infected patients should have hematocrit measured once a week until hematocrit has been stabilized, and measured periodically thereafter.

Dose or Diminished Responsiveness: If the patient fails to respond or to maintain a response, the following tolerologies should be considered and evaluated:

1) Iron deficiency: functional iron deficiency may develop with normal ferritin levels but low transferrin saturation (less than 20%), presumably due to the inability to mobilize iron stores rapidly enough to support increased erythropoiesis. Virtually all patients will eventually require supplemental iron therapy.

2) Infection: infectious, inflammatory, or malignant processes

3) Occult blood loss.

4) Underlying hematologic diseases (i.e., thalassemia, refractory anemia, or other myelosclerotic disorders).

5) Vitamin deficiencies: folie acid or vitamin B12.

6) Aluminum intoxication.

7) Cereals fibrosa cystica.

In the future: Reviewing the INDICATIONS AND USAGE section such as "INDICATIONS AND USAGE:

Drug Interactions: No evidence of interaction of PROCRIT (Epoetina alfa) with other drugs was observed in the course of clinical trials.

Carcinoembryonic Antigen, Mutagenesis, and Impairment of Fertility: Carcinogenic potential of PROCRIT has not been evaluated. PROCRIT should be administered to male and female rats treated intravenously with PROCRIT, there was a trend for slightly increased fetal wastage at doses of 100 and 500 U/kg.

Pregnancy Category C: PROCRIT has been shown to have adverse effects in rats when given in doses five times the human dose. There are no adequate and well-controlled studies in pregnant women, if the dose of PROCRIT is used during pregnancy only if potential benefits justify the potential risk to the fetus.

In studies in female rats, there were decreases in body weight gain, delays in appearance of vaginal dilation, delayed or absent estrous cycles, and an increased number of cervical corpora lutea in the F1 fetuses of the 500 U/kg group. In female rats treated intravenously, there was a trend for slightly increased fetal wastage at doses of 500 U/kg. PROCRIT had no adverse effects at doses as high as 500 U/kg in pregnant rabbits (from day 6 to 18 of gestation).

Nutritional: Postnatal observations of the live offspring (F1 generation) of female rats treated with PROCRIT during gestation and lactation revealed no effect of PROCRIT at doses of up to 500 U/kg. There were, however, decreases in body weight gain and a delay in the appearance of normally open eyes in the F1 offspring of the 100 U/kg group. The number of cervical corpora lutea in the F1 fetuses of the 500 U/kg group. There were no PROCRIT-related effects on the F2 generation fetuses.

It is not known whether PROCRIT is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PROCRIT is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of PROCRIT in children have not been established.

Chronic Renal Failure Patients

Patients with CRF Not Requiring Dialysis: Blood pressure and hematocrit should be controlled before therapy. Blood pressure should be controlled adequately before initiation of therapy. Blood pressure during PROCRIT therapy, often during the early phase of treatment when the hematocrit is increasing.

For patients who respond to PROCRIT with a rapid increase in hematocrit (e.g., more than 4 points in any two-week period), the dose of PROCRIT should be reduced because of the possible association of excessive rate of rise of hematocrit with an exacerbation of hypertension.

Seizures: Seizures have occurred in patients with CRF participating in PROCRIT clinical trials.

In patients on dialysis, there was a higher incidence of seizures during the first 90 days of therapy (primarily in approximately 2.5% of patients as compared with later timepoints. Given the potential for an increased risk of seizures during the first 90 days of therapy, blood pressure and the presence of premonitory neurolgic symptoms should be monitored closely. Patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy machinery during this period.

Thrombotic Events: During hemodialysis, patients treated with PROCRIT may require increased anticoagulation with heparin to prevent clotting of the artificial kidney. Clotting of the tunneled venous V-V shunt has occurred at an annualized rate of about 0.25 events per patient-year on PROCRIT therapy overall. For patients with CRF (whether on dialysis or not), other thrombotic events (e.g., myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis) have occurred at an annualized rate of less than 0.04 events per patient-year on PROCRIT therapy. Patients with pre-existing vascular disease should be monitored closely.

In contrast to CRF patients, PROCRIT therapy has not been linked to exacerbation of hypertension, seizures, and thrombotic events in HIV-infected patients.

In some female patients, menses have resumed following PROCRIT therapy; the possibility of potential pregnancy should be discussed and the need for contraception evaluated.

In some clinical studies in dogs and rats, but not in monkeys, PROCRIT therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The daily dose of PROCRIT may result in bone marrow fibrosis in a matched group of patients who had not been treated with PROCRIT.
nitrogen (BUN), creatinine, phosphorus, and potassium) in PROCRIT (Epoetin alfa) -treated patients should be monitored regularly to assure the adequacy of the dialysis prescription.

Renal Function: In patients with CRF not on dialysis, renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients. In patients with CRF not on dialysis, placebo-controlled studies demonstrated a progression of renal function over periods of greater than one year have not been completed. In shorter-term trials in patients with CRF not on dialysis, changes in creatinine and creatinine clearance were not significantly different in PROCRIT-treated patients, compared with placebo-treated patients. Analysis of the slope of 1/serum creatinine vs. time plots in these patients indicates no significant change in the slope after the initiation of PROCRIT therapy.

AZT-treated HIV-infected Patients

Hypertension: Exacerbation of hypertension has not been observed in AZT-treated HIV-infected patients treated with PROCRIT. However, PROCRIT should be withheld in these patients if pre-existing hypertension is uncontrolled, and should not be started until blood pressure is controlled. In double-blind studies, a single seizure has been experienced by a PROCRIT-treated patient.

ADVERSE REACTIONS

Chronic Renal Failure Patients

Studies analyzed to date indicate that PROCRIT is generally well-tolerated. The adverse events noted are similar to those experienced by patients not receiving PROCRIT. In double-blind, placebo-controlled studies involving over 300 patients with CRF, the events reported in greater than 5% of PROCRIT-treated patients during the blinded phase were:

- Percent of Patients Reporting Event

<table>
<thead>
<tr>
<th>Event</th>
<th>PROCRIT-Treated Patients</th>
<th>Placebo-Treated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>CVA/TIA</td>
<td>0.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>MI</td>
<td>0.6%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

In the U.S. PROCRIT studies in patients on dialysis (over 567 patients) the incidence (number of events per patient-year) of the most frequently reported adverse events were: nausea (0.25%), headache (0.40%), decreased appetite (0.31), nausea vomiting (0.25), and clogged vascular access (0.25), shortness of breath (0.14), hyperkalemia (0.11), and diarrhea (0.11). Other reported events occurred at a rate of less than 0.10 events per patient per year.

Events reported to have occurred within several hours of administration of PROCRIT were rare, mild and transient, and included flu-like symptoms such as arthralgias and myalgias.

In all studies analyzed to date, PROCRIT administration was generally well tolerated, irrespective of the route of administration.

Allergic Reactions: There have been no reports of serious allergic reactions or anaphylaxis associated with PROCRIT administration. Skin rashes and urticaria have been observed rarely and when reported have been mild and transient in nature. There has been no evidence of development of antibodies to erythropoietin patients tested to date, including those receiving intravenous PROCRIT for over two years. Nevertheless, if an anaphylactic reaction occurs, PROCRIT should be immediately discontinued and appropriate therapy initiated.

Seizures: There have been 47 seizures in 1010 patients on dialysis treated with PROCRIT with an exposure of 986 patient-years for a rate of approximately 0.045 events per patient-year. However, there appeared to be a higher rate of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients), when compared to subsequent 90-day time periods. The relationship, if any, of PROCRIT therapy to seizures is uncertain. The baseline incidence of seizures in the untreated dialysis population is difficult to determine; it appears to be in the range of 5-10% per patient-year.

Hypertension: Increases in blood pressure have been reported in clinical trials, often during the first 90 days of therapy. When data from all patients in the U.S. Phase III multicenter trial were analyzed, there was an apparent trend of more reports of hypertensive adverse events in patients on dialysis with a faster rate of rise in hematocrit (greater than 4 hematocrit points in any two week period). However, in a double-blind, placebo-controlled, hypertensive adverse events were not reported at an increased rate in the PROCRIT-treated group (150 U/kg T.I.W.) relative to the placebo group.

Thrombotic Events: Clotting of the vascular access has occurred at an annualized rate of about 0.25 events per patient-year on PROCRIT therapy.

Overall, for patients with CRF (whether on dialysis or not), other thrombotic events (e.g., myocardial infarction, cerebrovascular accident, transient ischemic attack) have occurred at an annualized rate of less than 0.04 events per patient-year of PROCRIT therapy.

AZT-treated HIV-infected Patients

Adverse experiences reported in clinical trials with PROCRIT in AZT-treated HIV-infected patients consist with the progression of HIV infection. In double-blind, placebo-controlled studies of 3-months duration involving approximately 300 AZT-treated HIV-infected patients, adverse events with an incidence of ≥ 10% in either PROCRIT-treated patients or placebo-treated patients were:

<table>
<thead>
<tr>
<th>Percent of Patients Reporting Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROCRIT-Treated Patients</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Rash</td>
</tr>
</tbody>
</table>
Introducing...

OMNIFLOX
(emaflaxacin HCl)
OMNIFLAX™ (temafloxacin hydrochloride)
Filmtab® Tablet

BRIEF SUMMARY
CONTRAINDICATIONS FOR FULL PRESCRIBING INFORMATION
INDICATIONS AND USAGE
OMNIFLAX™ is contraindicated in the treatment of mild to moderate adult infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Acute Bacterial Exacerbation of Chronic Bronchitis caused by Haemophilus influenzae, Moraxella (brunneum) catarrhalis, and Moraxella noncatarrhalis.

For treatment of pneumonia caused by Haemophilus influenzae or Streptococcus pneumoniae.

Pneumonia caused by Escherichia coli, Klebsiella pneumonie, or Proteus mirabilis.

Uncomplicated Skin and Skin Structure Infections caused by Acinetobacter calcoaceticus, Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus.

Uncomplicated Urinary Tract Infections (cystitis) caused by Escherichia coli, Proteus mirabilis, and Staphylococcus epidermidis.

Complicated Urinary Tract Infections caused by Escherichia coli, or Klebsiella pneumonie.

For combination therapy for serious skin and skin structure infections caused by S. aureus (including MRSA) and gram-negative bacteria.

CONTRAINDICATIONS
Temafloxacin should not be used in patients with a history of hypersensitivity to temafloxacin or to any of the following groups of antibacterial agents:

ANSWER:

OMNIFLAX™ SHOULD NOT BE USED IN CHILDREN, ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, and LACTATING WOMEN. (SEE PREGNANCY AND LACTATION IN PRECAUTIONS.)

NURSING MOTHERS SUBSTANCES IN THE PRECAUTIONS SECTION.)

The oral administration of temafloxacin 150 mg/day (7 times the maximum daily human dose) for one week caused increases in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent changes of the cartilage. Other joints also produced lesions of weight-bearing joints and other signs of arthritis in immatures of various species (See ANIMAL PHARMACOLOGY).

Serious and occasionally totally temporary (unpredictable or unprovoked) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, photophobia or facial edema, dyspnea, urticaria, or itching.

Only a few of these patients had a history of hypersensitivity reactions. Serious hypersensitivity reactions have also been reported following treatment with temafloxacin. If an allergic reaction to temafloxacin occurs, discontinue the drug. Serious allergic reactions may require immediate emergency treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and intravenous or subcutaneous hydrocortisone, as indicated.

Conversions were reported in one patient in temafloxacin clinical trials (a patient with a known severe drug allergy) who reacted to temafloxacin with urticarial rash, laryngospasm, and bronchospasm. The patient had a history of urticarial rash and bronchospasm following anaphylactic reactions.

Conversions had been reported in patients receiving temafloxacin, the drug should be discontinued and appropriate measures instituted.

The oral administration of temafloxacin 150 mg/day (7 times the maximum daily human dose) for one week in dogs has been demonstrated.

Temafloxacin does not affect blood flow, cerebral oxygen metabolism, or cerebral blood uptake in the central nervous system (CNS) based on positron emission tomography. However, until more information becomes available, temafloxacin, like all other quinolones, should be used with caution in patients with known or suspected CNS irritation, especially if there are cerebrovascular, epilepsy, or other factors which predispose to seizures. (See ADVERSE REACTIONS.)

Acute and chronic use of temafloxacin has been demonstrated.

Temafloxacin does not affect blood flow, cerebral oxygen metabolism, or cerebral blood uptake in the central nervous system (CNS) based on positron emission tomography. However, until more information becomes available, temafloxacin, like all other quinolones, should be used with caution in patients with known or suspected CNS irritation, especially if there are cerebrovascular, epilepsy, or other factors which predispose to seizures. (See ADVERSE REACTIONS.)

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Acute and chronic use of temafloxacin has been demonstrated.
Can the combination of a monobactam and a penicillin replace the classic combination of a β-lactam agent and an aminoglycoside?


This open, comparative, randomized study compared the efficacy of the combination of aztreonam and either cloxacillin or oxacillin with the combination of tobramycin and either cefuroxime or cefotaxime as empiric therapy. The addition of metronidazole was allowed if anaerobic pathogens were suspected. All patients

Percent

Clinical cure Mortality

100

90

80

70

60

50

40

30

20

10

0

P<0.05

Aztreonam/cloxacillin

(n=41)

Tobramycin/cephalosporin

(n=35)

P=NS

Adapted from Colardyn et al.

had serious, largely pulmonary infections and received ventilatory support. Patients with urinary tract infection were included only if concomitant septicemia was suspected. The study was conducted in 2 medical intensive care units. Only adult medical patients with a suspected or proven serious bacterial infection (excluding cardiac care and trauma patients) were enrolled. Empiric therapy was started only in previously untreated patients after admission to the ICU.

The results of this study showed a significant difference in cure rate between the 2 combinations. The aztreonam group experienced an 80% clinical cure rate with mortality of 15%. The aminoglycoside regimen produced a 51% clinical cure rate with 23% mortality. Because of the small size (76 evaluable patients) and heterogeneity of the study group, this difference must be confirmed in larger clinical trials.

The excellent clinical results achieved with the aztreonam regimen were not compromised by adverse reactions. The most important drug-related adverse effect in this study was new onset nephrotoxicity, which occurred in 11% (2/18) of patients in the aminoglycoside group and none of the patients in the aztreonam group. Superinfection was observed in 20% (7/35) of patients in the aminoglycoside group and in only 2% (1/41) of patients in the aztreonam group.

"These excellent results may lead to the replacement of an aminoglycoside with aztreonam for use in combination with another β-lactam antibiotic."

Following IV administration of AZACTAM, the most commonly seen adverse reactions occurred in less than 2% of patients, including local reactions, diarrhea, nausea/vomiting, and rash.

For a complete discussion of INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS, please see brief summary of prescribing information on following page.

Azactam®

aztreonam IV/IM 1g/2g

A logical alternative to aminoglycosides.
AZACTAM® FOR INJECTION
Aztreonam For Injection

DESCRIPTION-AZACTAM (Aztreonam, Squibb) is the first member of a new class of antibiotics classified as monobactams. AZACTAM is a totally synthetic bacterial cell wall antibiotic with activity against a wide spectrum of gram-negative aerobic pathogens. The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other beta-lactam antibiotics. Aztreonam is a sterile, nonpyrogenic, sodium-free, white to yellowish-white lyophilized cake, containing approximately 780 mg aztreonam per gram of aztreonam for intramuscular or intravenous use following reconstitution with sterile water for injection.

ACUTE TOXICITY—Aztreonam has not been shown to have a 

pH in the range of 4.5-7.5.

INDICATIONS AND USAGE—Before initiating treatment with AZACTAM, appropriate specimens should be obtained for isolation of the causative organism(s) and for determination of susceptibility to aztreonam. Treatment with AZACTAM may be started empirically before results of the susceptibility testing are available; subsequently, appropriate antibiotic therapy should be continued.

AZACTAM For Injection is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms: Urinary Tract Infections (complicated and uncomplicated), including pyelonephritis and cystitis (initial and recurrent) caused by Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Enterobacter cloacae, Klebsiella oxytoca*, Citrobacter species* and Serratia marcescens.* Lower Respiratory Tract Infections, including pneumonia and bronchitis caused by Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Haemophilus influenzae, Proteus mirabilis, Enterobacter species and Serratia marcescens.* Septicemia caused by Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis*, Serratia marcescens* and Enterobacter species. Skin and Skin-Structure Infections, including those associated with postoperative wounds, ulcers and burns caused by Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Citrobacter species.* Intra-abdominal Infections, including peritonitis caused by Escherichia coli, Klebsiella species, including P. aeruginosa, Enterobacter species* and Citrobacter species* including C. freundii* and Serratia species* including S. marcescens.* Gynecologic Infections, including endometritis and pelvic cellulitis caused by Escherichia coli, Klebsiella pneumoniae*, Enterobacter species* including E. cloacae* and Proteus mirabilis*.

AZACTAM is indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscus perforations, cutaneous infections and infections of serous surfaces. AZACTAM is effective against most of the commonly encountered gram-negative aerobic pathogens seen in general surgery.

Concurrent Therapy—Concurrent initial therapy with other antimicrobial agents and AZACTAM is recommended before the causative organism(s) is known in seriously ill patients who are also at risk of having an infection due to gram-positive aerobic pathogens. If anaerobic organisms are also suspected, therapy should be initiated using an anti-anaerobic agent concurrently with AZACTAM. Certain antibiotics (e.g., cefoxitin, imipenem) may induce high levels of beta-lactamase in vitro in some gram-negative, aerobic organisms such as Enterobacter and Pseudomonas species, resulting in antagonism to many beta-lactam antibiotics including aztreonam. These in vitro findings suggest that such beta-lactamase-inducing antibiotics should not be used concurrently with aztreonam. Following identification and susceptibility testing, appropriate antibiotic therapy should be continued.

CONTRAINDICATIONS—Aztreonam is contraindicated in patients with known allergy to this antibiotic.

WARNINGS-Pseudomembranous colitis has been reported with nearly all antibacterial agents, including aztreonam, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of Clostridium difficile, an opportunistic pathogen. Studies indicate that a toxin produced by C. difficile is the primary cause of "antibiotic-associated colitis." After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an oral antibacterial drug effective against C. difficile (e.g., vancomycin). Careful inquiry should be made for a history of hypersensitivity reaction to any antibiotic or other drugs. Antibiotics should be given with caution to any patient who has had sensitivity to this drug. It is important to ask about patients who have had immediate hypersensitivity reactions (e.g., anaphylactic or urticarial) to penicillins and/or cephalosporins should be followed with special care. If an allergic reaction to aztreonam occurs, discontinue the drug and institute other appropriate treatment (e.g., mast cell stabilizers, antihistamines, corticosteroids). Serious hypersensitivity reactions may require epinephrine and other emergency measures.

PRECAUTIONS—General: In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy. Aztreonam is used concurrently with aztreonam, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored in order to detect the potential nephrotoxic effects of the antimicrobial antibiotics. The use of antibiotics may promote the overgrowth of nonsusceptible organisms, including gram-positive organisms and fungi. Should superinfection occur during therapy, appropriate measures should be taken.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenic studies in animals have not been performed. Genetic toxicity studies performed in vivo and in vitro with aztreonam in several standard laboratory models revealed no evidence of mutagenic potential at the chromosomal or DNA level. Two-week, weak, headache, fever, diarrhea, rash at daily doses up to 20 times the maximum recommended human dose, prior to and during gestation and lactation, revealed no evidence of impaired fertility. There was a slightly reduced survival rate during the lactation phase. Hematologic, pathologic, skeletal, and hematopoietic abnormalities in rats that received the highest dosage, but not in offspring of rats that received five times the maximum recommended human dose.

Pregnancy—Pregnancy Category B: Aztreonam crosses the placenta and enters fetal circulation. Studies in pregnant rabbits and rats receiving daily doses up to 15 and 5 times, respectively, the maximum recommended human dose, revealed no evidence of embryo- or fetotoxicity or teratogenicity. No drug-induced changes were seen in any of the male rats receiving 15 times the maximum recommended human dose of aztreonam during late gestation and lactation. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed.

Nursing Mothers—Aztreonam is excreted in breast milk in concentrations that are less than 1% of concentrations determined in simultaneously obtained maternal serum; consideration should be given to temporary discontinuation of nursing and use of formula feedings.

Pediatric Use—Safety and effectiveness have not been established in infants and children.

ADVERSE REACTIONS—Local reactions such as phlebitis, thrombophlebitis following IV administration, and discomfort at the injection site following IM administration occurred at rates of approximately 1.9% and 2.4%, respectively. Systemic reactions (considered to be related to therapy or of uncertain etiology) occurring at an incidence of 1 to 1.3% include diarrhea, nausea and/or vomiting, and rash. Reactions occurring at an incidence of less than 1% are listed within each body system in order of decreasing severity: Hypersensitivity—urticaria, bronchospasm, Hematological—pancytopenia, neutropenia, thrombocytopenia, anemia, leukocytosis, thromboctysis, gastrointestinal—abdominal cramps, rare cases of C. difficile-associated diarrhea, including pseudomembranous colitis, or gastrointestinal bleeding have been reported. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Dermatologic—purpura, erythema multiforme, urticaria, exfoliative dermatitis, dermatitis, pruritus, diaphoresis. Cardiac—tachycardia, Hypo- and hypertension, transient. ECG changes (ventricular bigeminy and PVC). Respiratory—one patient experienced flushing, chest pain, and dyspnea. Hepatobiliary—hepatitis, jaundice, Nervous System—dizziness, insomnia. Musculoskeletal—muscular aches. Special Senses—tinnitus, diplopia, mouth ulcer, altered taste, numb tongue, sneezing and nasal congestion, Hallucinations—other. Coadministration of aztreonam with methotrexate may increase toxicity. Overdosage—If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis.

DOSEAGE AND ADMINISTRATION—Dosage adjustments are recommended for patients with impaired renal function. In elderly patients, estimates of creatinine clearance should be obtained and appropriate dosage modifications made if necessary.

HOW SUPPLIED—AZACTAM For Injection (Aztreonam For Injection)—Lyophilized—is supplied in single-dose 15 mL vials containing 500 mg, or 1 g/vial; in single-dose 30 mL vials containing 2 g/vial; and in single-dose 100 mL intravenous infusion bottles containing 500 mg or 1 g or 2 g/bottle.

Consult package insert before prescribing AZACTAM (aztreonam).


Issued: February 1992

(J-231E)
The easy way to MIC

1. Swab or flood bacterial suspension on agar plate.

2. Apply an E test strip and incubate.

3. Read exact MIC where inhibition zone intersects scale.

E test® is an antibiotic gradient strip used for direct determination of MIC. The scale of the strip represents a complete and continuous concentration range covering 15 two-fold dilutions.

E test can be applied to a majority of microorganisms grown on agar media, including rapid growers as well as anaerobes and other fastidious bacteria.

Contact your local distributor now for more information.

E test

AB Biodisk, Pyramidvägen 7, S-171 36 Solna, Sweden.
Tel. +46-8 730 07 60 Fax +46-8 83 81 58

E test is available through local distributors in the following countries:

Australia +61-2-567 5258 Austria +43-2240 7944 Belgium +32-2-666 0711 Brazil +55-11-284 52 33 Canada +1-416-868 0777 Denmark +45-42 811 129 Finland +358-0-452041

France +33-1-446 20860 Germany +49-38750 0731 Greece +30-1-630 48552 Iceland +354-1-956 666 Ireland +353-1-956 666 Italy +39-2-400 90222 Malaysia +60-37334988 N. Ireland +44-222 728 248 Norway +47-2-22 4068 Portugal +351-1-434 4844 Singapore +65-286 63 88 Spain +34-1-461 1051 Switzerland +41-37-315555 Taiwán +886-2-731 13 14 Thailand +662-221 2193 Turkey +90-2-141 63 51 U.K. +44-440 704 499 or +44-81-758 0991 USA +1-202 255 6730 or +1-800-874-8814
Now you can use NEUPOGEN®
(FILGRASTIM)
A recombinant G-CSF

...to specifically stimulate neutrophil production after myelosuppressive chemotherapy¹

- Promotes differentiation, maturation and production of neutrophils
- Shown to act specifically on both immature bone marrow progenitor cells and mature, differentiated neutrophils, in vivo

...to decrease the incidence of infection by reducing the duration of neutropenia¹

- Reduces the risk of infection as manifested by fever in association with neutropenia¹
- Shown to reduce hospitalizations for fever in association with neutropenia when compared to placebo
Well tolerated with minimal adverse effects

- Well tolerated — the majority of adverse effects reported in clinical trials were attributed to the underlying malignancy or chemotherapy

- No reports of effects that mimic infection such as fever or flu-like symptoms attributed to NEUPOGEN®

- Of adverse effects attributed to NEUPOGEN®, only medullary bone pain, usually mild to moderate and controllable with non-narcotic analgesics, occurred at a rate at least 5% greater than placebo

- No antibody development reported

- Contraindicated in patients with known hypersensitivity to E. coli-derived products

For more information...

Scientific or clinical information: Call your Amgen Sales Representative at 1-800-28-AMGEN (Monday through Friday, 6 AM-9 PM Pacific Time)

Or

Amgen Professional Services Department at 1-800-77-AMGEN (6 AM-6 PM Pacific Time — on call 24 hours)

Reimbursement information: General reimbursement information can be obtained through your Amgen Sales Representative. For case-by-case information, please call the NEUPOGEN Reimbursement Hotline, 1-800-272-9376 (in Washington, D.C., 202-637-6698), Monday through Friday, 9 AM-5 PM Eastern Time.

AMGEN®

Pioneers in Hematopoietic Growth Factors

*As manifested by febrile neutropenia (ANC <500 cells/mm³, temperature ≥ 38.2°C)

Please see following page for brief summary of Prescribing Information.
NEUPOGEN® (Filgrastim)  
Brief Summary of Prescribing Information

INDICATIONS AND USAGE
NEUPOGEN® is indicated to decrease the incidence of adverse effects, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs who are at a high risk for febrile neutropenia. A complete blood cell count and platelet count should be obtained prior to chemotherapy, and twice per week (see laboratory monitoring) during NEUPOGEN® treatment to avoid leukocytopenia and to monitor the neutrophil count. In Phase III clinical studies, NEUPOGEN® therapy was discontinued when the absolute neutrophil count (ANC) was <1,000/mm³ after the expected chemotherapy-induced nadir.

CONTRAINdications
NEUPOGEN® is contraindicated in patients known hypersensitivity to E. coli derived proteins.

WARNINGS
In patients who have received NEUPOGEN® to date, no serious adverse reactions that would limit the use of the product have been reported.

PRECAUTIONS
General
Simultaneous Use with Chemotherapy
The safety and efficacy of NEUPOGEN® given simultaneously with cytotoxic chemotherapy have not been established. When given simultaneously, the potential for additive myelosuppression exists. Use NEUPOGEN® in patients receiving simultaneous cytotoxic chemotherapy, do not use NEUPOGEN® in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy (see DOSAGE AND ADMINISTRATION).

The efficacy of NEUPOGEN® has not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression such as nitrosourea, mitomycin C or with myelosuppressive doses of anti-metabolites such as 5-fluorouracil or cytarabine arabinoside.

Growth Factor Potential
NEUPOGEN® is a growth factor that primarily stimulates neutrophils. However, the possibility that NEUPOGEN® can act as a growth factor for any tumor type, particularly myeloid malignancies, cannot be excluded. Therefore, because of the possibility of tumor growth, precuation should be exercised in using this drug in any malignancy with myeloid characteristics.

Leukocytosis
White blood cell counts of 100,000/mm³ or greater were observed in approximately 2% of patients receiving NEUPOGEN® at doses above 5 mg/kg/day. There were no reports of adverse events associated with this degree of leukocytosis. In order to avoid the potential complications of excessive leukocytosis, a complete blood count (CBC) is recommended twice per week during NEUPOGEN® therapy (see laboratory monitoring).

Premature Discontinuation of NEUPOGEN® Therapy
A small increase in the incidence of severe infections (requiring hospitalization) was noted after 2 to 6 days after initiation of NEUPOGEN®. For a sustained therapeutic response, NEUPOGEN® therapy should be continued until the post nadir ANC reaches 10,000/mm³. Therefore, the premature discontinuation of NEUPOGEN® therapy may delay the recovery from the time to achieve a post chemotherapy neutrophil nadir, is generally not recommended (see DOSAGE AND ADMINISTRATION).

Chronic Administration
The safety and efficacy of chronic administration of NEUPOGEN® have not been established. Preliminary investigational studies with NEUPOGEN® have been conducted in 224 patients with severe chronic neutropenia who have been treated for a median of 10 years. There were no reports of adverse events associated with this degree of chronic administration. NEUPOGEN®, % of patients were noted to have clinical or hematological. Less frequently observed adverse events include exacerbation of some pre-existing skin disorders (e.g., psoriasis, alopecia areata, hypertrichosis, thrombocytopenia [platelets less than 50,000/mm³] and osteoporosis.

OSS
In studies of NEUPOGEN® administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see ADVERSE REACTIONS). Because of the potential for recovering higher doses of chemotherapeutic agents (i.e., full doses on the prescribed schedule), the patient may be at greater risk for thrombocytopenia, anemia, and non-hematologic toxicities of cytotoxic chemotherapy (please refer to the prescribing information of the specific chemotherapy agents used). Regular monitoring of the hematocrit and platelet counts is recommended for patients receiving long-term administration of NEUPOGEN®. % of patients had noted to have clinical or hematological adverse events. Less frequently observed adverse events include exacerbation of some pre-existing skin disorders (e.g., psoriasis, alopecia areata, hypertrichosis, thrombocytopenia [platelets less than 50,000/mm³] and osteoporosis.

DIAGNOSIS
In studies of NEUPOGEN® administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see ADVERSE REACTIONS). Because of the potential for recovering higher doses of chemotherapeutic agents (i.e., full doses on the prescribed schedule), the patient may be at greater risk for thrombocytopenia, anemia, and non-hematologic toxicities of cytotoxic chemotherapy (please refer to the prescribing information of the specific chemotherapy agents used). Regular monitoring of the hematocrit and platelet counts is recommended for patients receiving long-term administration of NEUPOGEN®. % of patients had noted to have clinical or hematological adverse events. Less frequently observed adverse events include exacerbation of some pre-existing skin disorders (e.g., psoriasis, alopecia areata, hypertrichosis, thrombocytopenia [platelets less than 50,000/mm³] and osteoporosis.

Diagnosis
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Laboratory Monitoring
A CBC and platelet count should be obtained prior to chemotherapy, and at regular intervals (twice per week) during NEUPOGEN® therapy. Following cytotoxic chemotherapy, the nadir is usually observed earlier during cycles when NEUPOGEN® was administered, and white blood cell differentials demonstrated a left shift, including the appearance of promyelocytes and myeloblasts. In addition, the duration of severe neutropenia was reduced, and was followed by an accelerated recovery in the neutrophil counts. Therefore, routine monitoring of white blood cell counts, particularly at the time of the recovery from the post chemotherapy nadir, is recommended in order to avoid excessive leukocytosis.

Drug Interaction
No evidence of interaction of NEUPOGEN® with other drugs was observed in the course of clinical trials.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of NEUPOGEN® has not been studied. NEUPOGEN® failed to induce bacterial gene mutation either by the presence or absence system. NEUPOGEN® had no observed effect on the fertility of male or female rats, or on general reproductive parameters in rats.

Pharmacology
NEUPGEN® has been shown to have adverse effects in pregnant rabbits when given in doses 2 to 3 times the human therapeutic doses to pregnant women. NEUPOGEN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In chicks, the effects were noted on the development of visceral organs in the yolk sac. In rats, after exposure in the period of organogenesis at doses between 3 and 5 mg/kg.

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INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by the susceptible organisms listed below.

LOWER RESPIRATORY TRACT INFECTIONS caused by Streptococcus pneumoniae, Streptococcus pyogenes (including strains resistant to penicillin), Haemophilus influenzae, Moraxella catarrhalis, and Mycoplasma pneumoniae.

SKIN AND SKIN STRUCTURE INFECTIONS caused by Staphylococcus aureus, Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, and Pseudomonas aeruginosa.

URINARY TRACT INFECTIONS (uncomplicated and uncomplicated) caused by E. coli, Proteus mirabilis, and Pseudomonas aeruginosa.

NONTUBERCULOUS INTRATHORACIC INFECTIONS caused by Mycobacterium avium intracellulare in patients infected with HIV.

GUARDIAN I (IVM) ceftriaxone sodium Roche

Rocephin is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed:

LOCAL REACTIONS — pain, induration or tenderness at the site of injection (1%). Less frequently reported (less than 1%) was phlebitis after I.V. administration.

HYPERSensitivity — rash (1%). Less frequently reported (less than 1%) were pruritus, fever and chills.

HEMATOLOGIC — eosinophilia (6%), thrombocytopenia (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

GASTROINTESINAL — diarrhea (2.7%). Less frequently reported (less than 1%) were nausea or vomiting, anorexia and dyspepsia. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

HEPATIC — elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (less than 1%) were jaundice, cholestasis, and hepatitis.

RENAL — elevations of the BUN (1.2%). Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine.

CENTRAL NERVOUS SYSTEM — headache or dizziness were reported occasionally (less than 1%).

GENITOURINARY — micturition or vaginal irritation were reported occasionally (less than 1%).

MISCELLANEOUS — diaphoresis and flushing were reported occasionally (less than 1%).

Other rare adverse observed reactions (less than 0.1%) include leukopenia, lymphocytosis, monocytosis, basophilia, a decrease in the platelet count, jaundice, anemia, neutropenia, lymphopenia, thrombocytopenia, and prolongation of the prothrombin time.

Rocephin therapy should be continued for at least two days after clearance of the signs and symptoms of infection have disappeared. The usual duration is 4 to 14 days; in complicated infections longer therapy may be required. Rocephin therapy should be continued for at least ten days.

Rocephin should not be used in patients with renal impairment; however, blood levels should be monitored in patients with severe renal impairment (e.g., dialysis patients) and in patients with both renal and hepatic dysfunctions.

Rocephin is supplied as a sterile crystalline powder in glass vials and piggyback bottles. The following packages are available:

- Vials containing 250 mg, 500 mg, 1 g or 2 g of ceftriaxone sodium, and 2 g or 4 g of ceftriaxone sodium in single dose plastic containers. (See following).

- 1 g of ceftriaxone sodium, isosomatic with approximately 1.9 g dextrose hydrolysate, USP added.

- 2 g of ceftriaxone sodium, isosomatic with approximately 1.2 g dextrose hydrolysate added.

Rocephin is a registered trademark of Abbott Laboratories, Inc.

Manufactured for Roche Laboratories, a division of Hoffmann-La Roche Inc., by Travelen Laboratories, Inc., Deerfield, Illinois 60015.

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Once-a-day

Rocephin® IV·IM
ceftriaxone sodium/Roche

Usual adult daily dosage: 1 to 2 gm once a day
Please see adjacent page for summary of product information.

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