

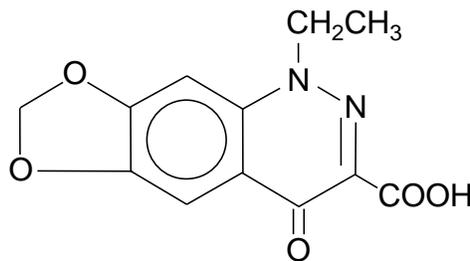
PV 1354-A UCP

Cinobac[®] Cinoxacin, USP

DESCRIPTION

Cinobac[®] (Cinoxacin, USP) is a synthetic antibacterial agent for oral administration. Cinoxacin, a quinolone, is 1-ethyl-1,4-dihydro-4-oxo-[1,3] dioxolo [4,5-g] cinnoline-3-carboxylic acid and occurs as white or very light-yellow, needle-shaped crystals. Cinobac is available as 250- (0.95 mmol) and 500-mg (1.9 mmol) capsules. These capsules also contain D & C Yellow No. 10, F D & C Blue No. 1, F D & C Red No. 3, F D & C Yellow No. 6, gelatin, silicon dioxide, silicone fluid, sodium lauryl sulfate, starch, titanium dioxide, and other inactive ingredients.

The molecular formula is $C_{12}H_{10}N_2O_5$ and the molecular weight is 262.22. The structural formula is:



CLINICAL PHARMACOLOGY

Cinoxacin is rapidly absorbed after oral administration. In fluorometric assay, a 500-mg dose produced a peak serum concentration of 15 $\mu\text{g/mL}$, which declined to approximately 1 to 2 $\mu\text{g/mL}$ 6 hours after administration. A 500-mg dose produced an average urine concentration of approximately 300 $\mu\text{g/mL}$ during the first 4 hours and approximately 100 $\mu\text{g/mL}$ during the second 4-hour period. These urine concentrations are many times greater than the minimal inhibitory concentration (MIC) of cinoxacin for most gram-negative organisms commonly found in urinary tract infections.

Ninety-seven percent of a 500-mg oral dose of radiolabeled cinoxacin was recovered in the urine within 24 hours, 60% of which was present as unaltered cinoxacin and the remainder as inactive metabolic products.

The presence of food did not affect the total absorption of cinoxacin. Peak serum concentrations were reduced by 30%, but the 24-hour urinary recovery of antibacterial activity was unaltered. The mean serum half-life is 1.5 hours.

Geriatric--Twenty geriatric patients (ages 70-89, 14 men and 6 women) with creatinine clearance from 58-80 mL/min, were given cinoxacin 500 mg every 12 hours for 7 days. Following the first dose of cinoxacin, the mean peak of the serum concentration was 14 $\mu\text{g/mL}$. Following the last dose, the mean peak of the serum concentration was 15 $\mu\text{g/mL}$. The mean urine

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concentration after 3 hours was 656 µg/mL, at 3-6 hr 1,234 µg/mL, and at 12 hours 33 µg/mL. The mean recovery of unaltered cinoxacin from the urine following the first dose and last dose was 55% and 62%, respectively.

Microbiology--Cinoxacin has *in vitro* activity against many gram-negative aerobic bacteria, particularly strains of *Enterobacteriaceae*. Cinoxacin inhibits bacterial deoxyribonucleic acid (DNA) synthesis, is bactericidal, and is active over the entire urinary pH range. Cross-resistance with nalidixic acid has been demonstrated.

Conventional chromosomal resistance to cinoxacin taken at recommended doses has been reported to emerge in approximately 4% of patients during treatment; however, bacterial resistance to cinoxacin has not been shown to be transferable via R-factor. Cinoxacin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections (*see* Indications and Usage):

Gram-negative aerobes:

- Enterobacter* species
- Escherichia coli*
- Klebsiella* species
- Proteus mirabilis*
- Proteus vulgaris*

Note: *Enterococcus* species, *Pseudomonas* species, and *Staphylococcus* species are resistant.

Susceptibility Tests--Diffusion Techniques: Quantitative methods that require measurement of zone diameters give an estimate of bacterial susceptibility. One such procedure is the National Committee for Clinical Laboratory Standards (NCCLS) approved procedure (M2-A5--Performance Standards for Antimicrobial Disk Susceptibility Tests 1993).¹ This method has been recommended for use with the 100-µg cinoxacin disk to test susceptibility to cinoxacin.

Interpretation involves correlation of the diameters obtained in the disk test with minimum inhibitory concentrations (MIC) for cinoxacin. Reports from the laboratory giving results of the standard single-disk susceptibility test with a 100-µg cinoxacin disk should be interpreted according to the following criteria (**these criteria only apply to isolates from urinary tract infections**):

<u>Zone diameter (mm)</u>	<u>Interpretation</u>
≥19	(S) Susceptible
15-18	(I) Intermediate
≤14	(R) Resistant

A report of "susceptible" indicates that the pathogen is likely to be inhibited by generally achievable urine levels. A report of "intermediate" indicates that the test results be considered equivocal or indeterminate. A report of "resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Certain strains of *Enterobacteriaceae* exhibit heterogeneity of resistance to cinoxacin. These strains produce isolated colonies within the inhibition zone. When such strains are encountered, the clear inhibition zone should be measured within the isolated colonies.

Standardized procedures require the use of laboratory control organisms. The 100-µg cinoxacin disk should give the following zone diameter:

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<u>Organism</u>	<u>Zone diameter (mm)</u>
<i>E. coli</i> ATCC 25922	26-32

Other quinolone antibacterial disks should not be substituted when performing susceptibility tests for cinoxacin because of spectrum differences between cinoxacin and other quinolones. The 100- μ g cinoxacin disk should be used for all *in vitro* testing of isolates.

Dilution Techniques: Broth and agar dilution methods, such as those recommended by the NCCLS (M7-A3--Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically 1993), may be used to determine the MIC of cinoxacin.² MIC test results should be interpreted according to the following criteria (**these criteria only apply to isolates from urinary tract infections**):

<u>MIC (μg/mL)</u>	<u>Interpretation</u>
≤ 16	(S) Susceptible
32	(I) Intermediate
≥ 64	(R) Resistant

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard cinoxacin powder should give the following MIC values:

<u>Organism</u>	<u>MIC range (μg/mL)</u>
<i>E. coli</i> ATCC 25922	2.0-8.0

INDICATIONS AND USAGE

Cinobac is indicated for the treatment of initial and recurrent urinary tract infections in adults caused by the following susceptible microorganisms: *Escherichia coli*, *Proteus mirabilis*, *Proteus vulgaris*, *Klebsiella* species (including *K. pneumoniae*), and *Enterobacter* species.

Cinobac is effective in preventing urinary tract infections for up to 5 months in women with a history of recurrent urinary tract infections.

In vitro susceptibility testing should be performed prior to administration of the drug and, when clinically indicated, during treatment.

CONTRAINDICATION

Cinobac is contraindicated in patients with a history of hypersensitivity to cinoxacin or other quinolones.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF CINOXACIN IN PEDIATRIC PATIENTS, PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (SEE PEDIATRIC USE, PREGNANCY, AND NURSING MOTHERS SUBSECTIONS IN THE PRECAUTIONS SECTIONS). The oral administration of a single 250-mg/kg dose of cinoxacin causes lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed lesions of the cartilage. Other quinolones also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone class antimicrobials. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of

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previous hypersensitivity reactions. If an allergic reaction to cinoxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management as clinically indicated.

Convulsions and abnormal electroencephalograms have been reported in a few patients receiving quinolone class antimicrobials. No causal relationship has been established. Convulsions, increased intracranial pressure, and toxic psychoses have also been reported in patients receiving other drugs in this class.

Quinolones may also cause central nervous system (CNS) stimulation with tremors, restlessness, light-headedness, confusion, or hallucinations. If these reactions occur in patients receiving cinoxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, cinoxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis, epilepsy, and other factors that predispose to seizures (*see* Adverse Reactions).

Achilles and other tendon ruptures that require surgical repair or resulted in prolonged disability have been reported with quinolones. Cinoxacin should be discontinued if the patient experiences pain, inflammation, or tendon rupture.

PRECAUTIONS

General--Since Cinobac is eliminated primarily by the kidney, the usual dosage should be lower in patients with reduced renal function (*see* Dosage and Administration). Administration of Cinobac is not recommended for anuric patients.

In clinical trials with large doses of quinolones, crystalluria was reported in some volunteers. Although crystalluria is not expected to occur with the usually recommended dosages of cinoxacin, patients should be well hydrated, and alkalinization of urine should be avoided.

Moderate to severe phototoxicity reactions have been observed in patients who were exposed to direct sunlight while receiving some members of this drug class. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Information for Patients--Patients should be advised that cinoxacin may be taken with or without meals. Patients should drink fluids liberally. **Antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or VIDEX[®] (didanosine) chewable/buffered tablets or the pediatric powder for oral solution may interfere with the gastrointestinal absorption of cinoxacin. These agents should be taken at least 2 hours before or 2 hours after cinoxacin administration. ~~Since sucralfate or antacids affect the absorption~~**

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~~of certain quinolones, patients should not take sucralfate or antacids within 2 hours of the administration of cinoxacin.~~

Patients should be advised to avoid excessive sunlight during cinoxacin therapy. If phototoxicity occurs, cinoxacin therapy should be discontinued.

Cinoxacin may be associated with hypersensitivity reactions following even a single dose. The drug should be discontinued at the first sign of skin rash or allergic reaction.

Cinoxacin can cause dizziness and light-headedness; therefore, patients should know how they react to the drug before operating an automobile or machinery or engaging in an activity requiring mental alertness or coordination.

Patients should be advised that convulsions have been reported in patients taking quinolones, including cinoxacin acid, and to notify their physician before taking this drug if there is a history of this condition.

Patients should be advised that cinoxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed during cinoxacin therapy.

Drug Interactions--Elevated plasma levels of theophylline have been reported with concomitant use of some quinolones. There have been reports of theophylline-related side-effects in patients on concomitant theophylline-quinolone therapy. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

Quinolones have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life. Although this interaction has not been reported with cinoxacin, caution should be exercised when cinoxacin is given concomitantly with caffeine-containing products.

Antacids or sucralfate substantially interfere with the absorption of some quinolones, resulting in low urine levels. Also, concomitant administration of quinolones with products containing iron, ~~or~~ multivitamins containing zinc, or Videx (didanosine)

chewable/buffered tablets or the pediatric powder for oral solution may result in low urine levels.

Quinolones, including cinoxacin, may enhance the effects of oral anticoagulants, such as warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

Seizures have been reported in patients taking another quinolone class antimicrobial and the nonsteroidal anti-inflammatory drug fenbufen concurrently. Animal studies also suggest an increased potential for seizures when these 2 drugs are given concomitantly. Fenbufen is not approved in the United States at this time. Physicians are provided this information to increase awareness of the potential for serious interactions when cinoxacin and certain nonsteroidal anti-inflammatory agents are administered concomitantly.

Elevated cyclosporine serum levels have been reported with the concomitant use of quinolones and cyclosporine.

Pregnancy--Teratogenic Effects--Pregnancy Category C--Reproduction studies have been performed in rats and rabbits at doses up to 10 times the daily human dose and have revealed no

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evidence of impaired fertility or harm to the fetus due to cinoxacin. There are, however, no adequate and well-controlled studies in pregnant women. Cinoxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (*see Warnings*).

Nursing Mothers--It is not known whether cinoxacin is excreted in human milk. Because other drugs in this class are excreted in human milk and because of the potential for serious adverse reactions from cinoxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use—**The safety and effectiveness of cinoxacin** in pediatric patients and adolescents less than 18 years of age have not been established.

Cinoxacin causes arthropathy in juvenile animals (*see Warnings*).

Geriatric Use--Following a single 500 mg dose of cinoxacin, peak serum concentrations in geriatric patients were similar to those in all adults. With repeated administration of cinoxacin, no accumulation of drug was found in the twenty patients ages 70-89 (*see Geriatric* under Clinical Pharmacology). No dosage adjustment is required based on age alone. In geriatric patients with reduced renal function, the dosage should be reduced (*see Impaired Renal Function* under Dosage and Administration).

Clinical studies of cinoxacin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

In clinical studies involving 1,118 patients, the following adverse effects were considered to be related to cinoxacin therapy:

Gastrointestinal--Nausea was reported most commonly and occurred in less than 3 in 100 patients. Other side effects, occurring less frequently (1 in 100), were anorexia, vomiting, abdominal cramps/pain, perverse taste, and diarrhea.

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Central Nervous System--The most frequent side effects were headache and dizziness, reported by 1 in 100 patients. Other adverse reactions possibly related to Cinobac include insomnia, drowsiness, tingling sensation, perineal burning, photophobia, and tinnitus. These were reported by less than 1 in 100 patients.

Hypersensitivity--Rash, urticaria, pruritus, edema, angioedema, and eosinophilia were reported by less than 3 in 100 patients. Rare cases of anaphylactic reactions have been reported. Toxic epidermal necrolysis has been reported very rarely. Erythema multiforme and Stevens-Johnson syndrome have been reported with cinoxacin and other drugs in this class.

Hematologic--Rare reports of thrombocytopenia.

Laboratory values reported to be abnormal were, in descending order of frequency, elevation of BUN (1 in 100), AST (SGOT), ALT (SGPT), serum creatinine, and alkaline phosphatase; and reduction in hematocrit/hemoglobin (each less than 1 in 100).

Although not observed in the 1,118 patients treated with cinoxacin, the following side effects have been reported for other drugs in the same pharmacologically active and chemically related class: restlessness, nervousness, change in color perception, difficulty in focusing, decrease in visual acuity, double vision, weakness, constipation, erythema and bullae, feelings of disorientation or agitation or acute anxiety, palpitation, soreness of the gums, joint stiffness, swelling of the extremities, and toxic psychosis or convulsions (rare). All adverse reactions observed with drugs in this class were reversible.

The most frequently reported adverse events in postmarketing surveillance of cinoxacin have been rash and anaphylactic reactions. Other frequently reported reactions have been pruritus, urticaria, allergic reactions, nausea, abdominal pain, and headache.

OVERDOSAGE

Signs and Symptoms--Symptoms following an overdose of cinoxacin may include anorexia, nausea, vomiting, epigastric distress, and diarrhea. The severity of the epigastric distress and the diarrhea are dose related. Headache, dizziness, insomnia, photophobia, tinnitus, and a tingling sensation have been reported in some patients. If other symptoms are present, they are probably secondary to an underlying disease state, an allergic reaction, or the ingestion of a second medication with toxicity.

Treatment--In all cases of suspected overdose, call your regional Poison Control Center to obtain the most up-to-date information about the treatment of overdose. This recommendation is made because, in general, information regarding the treatment of overdose may change more rapidly than do package inserts.

In managing overdose, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Patients who have ingested an overdose of cinoxacin should be kept well hydrated to prevent crystalluria.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of, or in addition to, gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of cinoxacin.

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DOSAGE AND ADMINISTRATION

The usual adult dosage for the treatment of urinary tract infections is 1 g daily, administered orally in 2 or 4 divided doses (500 mg b.i.d. or 250 mg q.i.d. respectively) for 7 to 14 days.

Doses should be administered at least 2 hours before or 2 hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or Videx (didanosine) chewable tablets or the pediatric powder for oral solution. Although susceptible organisms may be eradicated within a few days after therapy has begun, the full treatment course is recommended.

Impaired Renal Function--When renal function is impaired, a reduced dosage must be employed. After an initial dose of 500 mg, a maintenance dosage schedule should be used (*see table*).

MAINTENANCE DOSAGE GUIDE
FOR PATIENTS WITH RENAL IMPAIRMENT

<u>Creatinine Clearance</u> mL/min/1.73 m ²	<u>Renal Function</u>	<u>Dosage</u>
>80	Normal	500 mg b.i.d.
80-50	Mild Impairment	250 mg t.i.d.
50-20	Moderate Impairment	250 mg b.i.d.
<20	Marked Impairment	250 mg q.d.

Administration of Cinobac to anuric patients is not recommended.

When only serum creatinine is available, the following formula (based on sex, weight, and age of patient) may be used to convert this value into creatinine clearance.

The serum creatinine should represent a steady state of renal function.

$$\text{Males: } \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}}$$

$$\text{Females: } 0.9 \times \text{male value}$$

Preventive Therapy--A single dose of 250 mg at bedtime for up to 5 months has been shown to be effective in women with a history of recurrent urinary tract infections.

HOW SUPPLIED

Capsules:

250 mg, orange and green, imprinted with "OCL 55" on the cap and "CINOAC 250 mg" on the body, (UC 5355)--(40s) NDC 55515-055-02

Cinobac[®] (Cinoxacin, USP)

500 mg, orange and green, imprinted with "OCL 56" on the cap and "CINOBAC 500 mg" on the body, (UC 5356)--(50s) NDC 55515-056-04

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

ANIMAL PHARMACOLOGY

Crystalluria, sometimes associated with secondary urinary tract pathology, occurs in laboratory animals treated orally with cinoxacin. In the rhesus monkey, crystalluria (without urinary tract pathology) has been noted at doses as low as 50 mg/kg/day (lowest dose tested). Cinoxacin-related crystalluria has not been observed in humans receiving twice the recommended daily dosage.

Cinoxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested (*see* Warnings).

Some drugs of this class have been shown to have oculotoxic potential. Cinoxacin administered to cats at high dosages (200 mg/kg/day) resulted in retinal degeneration and other ocular changes. The dog appeared to be somewhat resistant to these effects, but high dosages (500 mg/kg/day) resulted in mild retinal atrophy. No cinoxacin-related ocular changes were noted in rabbit, rat, monkey, or human studies. (In one of the studies involving the monkey, cinoxacin was administered for 1 year at 10 times the recommended clinical dose.)

REFERENCES

1. National Committee for Clinical Laboratory Standards, Performance standards for antimicrobial disk susceptibility tests--5th ed. Approved Standard NCCLS Document M2-A5, Vol 13, No 24, NCCLS, Villanova, PA, 1993.
2. National Committee for Clinical Laboratory Standards, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically--3rd ed. Approved Standard NCCLS Document M7-A3, Vol 13, No 25, NCCLS, Villanova, PA, 1993.

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