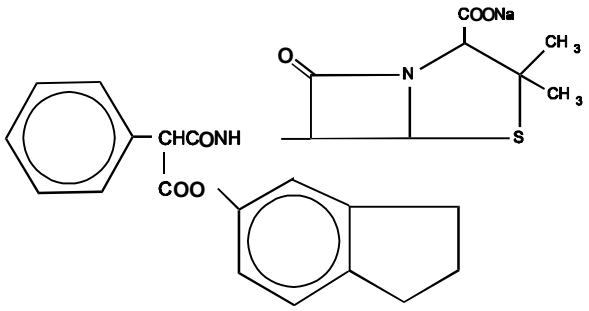
GEOCILLIN®
carbenicillin indanyl sodium
TABLETS
For Oral Use

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Geocillin® and other antibacterial drugs, Geocillin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Geocillin, a semisynthetic penicillin, is the sodium salt of the indanyl ester of Geopen® (carbenicillin disodium). The chemical name is: 1-(5-Indanyl)-N-(2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] hept-6-yl)-2-phenylmalonamate monosodium salt.

The structural formula is:



The empirical formula is: $C_{26}H_{25}N_2NaO_6S$ and mol. wt. is 516.55.

Geocillin tablets are yellow, capsule-shaped and film-coated, made of a white crystalline solid. Carbenicillin is freely soluble in water. Each Geocillin tablet contains 382 mg of carbenicillin, 118 mg of indanyl sodium ester. Each Geocillin tablet contains 23 mg of sodium.

Inert ingredients are: glycine; magnesium stearate and sodium lauryl sulfate. May also include the following: hydroxypropyl cellulose; hypromellose; opaspray (which may include Blue 2 Lake, Yellow 6 Lake, Yellow 10 Lake, and other inert ingredients); opadry light yellow (which may contain D&C Yellow 10 Lake, FD&C Yellow 6 Lake and other inert ingredients); opadry clear (which may contain other inert ingredients).

CLINICAL PHARMACOLOGY

Free carbenicillin is the predominant pharmacologically active fraction of Geocillin. Carbenicillin exerts its antibacterial activity by interference with final cell wall synthesis of susceptible bacteria.

Geocillin is acid stable, and rapidly absorbed from the small intestine following oral administration. It provides relatively low plasma concentrations of antibiotic and is primarily excreted in the urine. After absorption, Geocillin is rapidly converted to carbenicillin by hydrolysis of the ester linkage. Following ingestion of a single 500 mg tablet of Geocillin, a peak carbenicillin plasma concentration of approximately 6.5 mcg/ml is reached in 1 hour. About 30% of this dose is excreted in the urine unchanged within 12 hours, with another 6% excreted over the next 12 hours.

In a multiple dose study utilizing volunteers with normal renal function, the following mean urine and serum levels of carbenicillin were achieved:

		Mean Urine Concentration of Carbenicillin mcg/ml Hours After Initial Dose		
DRUG	DOSE	0–3	3–6	6–24
Geocillin	1 tablet q.6 hr	1130	352	292
Geocillin	2 tablets q.6 hr	1428	789	809

Mean serum concentrations of carbenicillin in this study for these dosages are:

		Mean Serum Concentration mcg/ml Hours After Initial Dose								
DRUG	DOSE	1/2	1	2	4	6	24	25	26	28
Geocillin	1 tablet q.6 hr	5.1	6.5	3.2	1.9	0.0	0.4	8.8	5.4	0.4
Geocillin	2 tablets q.6 hr	6.1	9.6	7.9	2.6	0.4	0.8	13.2	12.8	3.8

Microbiology

The antibacterial activity of Geocillin is due to its rapid conversion to carbenicillin by hydrolysis after absorption. Though Geocillin provides substantial *in vitro* activity against a variety of both gram-positive and gram-negative microorganisms, the most important aspect of its profile is in its antipseudomonal and antiproteal activity. Because of the high urine levels obtained following administration, Geocillin has demonstrated clinical efficacy in urinary infections due to susceptible strains of:

Escherichia coli
Proteus mirabilis
Proteus vulgaris
Morganella morganii (formerly *Proteus morganii*)
Pseudomonas species
Providencia rettgeri (formerly *Proteus rettgeri*)
Enterobacter species
Enterococci (*S. faecalis*)

In addition, *in vitro* data, not substantiated by clinical studies, indicate the following pathogens to be usually susceptible to Geocillin:

Staphylococcus species (nonpenicillinase producing)
Streptococcus species

Resistance

Most *Klebsiella* species are usually resistant to the action of Geocillin. Some strains of *Pseudomonas* species have developed resistance to carbenicillin.

Susceptibility Testing

Geopen (carbenicillin disodium) Susceptibility Powder or 100 μg Geopen Susceptibility Discs may be used to determine microbial susceptibility to Geocillin using one of the following standard methods recommended by the National Committee for Clinical Laboratory Standards:

M2-A3, "Performance Standards for Antimicrobial Disk Susceptibility Tests"
M7-A, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically"
M11-A, "Reference Agar Dilution Procedure for Antimicrobial Susceptibility Testing of Anaerobic Bacteria"
M17-P, "Alternative Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria"

Tests should be interpreted by the following criteria:

	Disk Diffusion Zone diameter (mm)		
Organisms	Suscept.	Intermed.	Resist.
Enterobacter	≥23	18–22	≤17
Pseudomonas sp.	≥17	14–16	≤13

	Dilution MIC (μg/ml)		
Organisms	Suscept.	Moderately Suscept.	Resist.
Enterobacter	≤16	32	≥64
Pseudomonas sp.	≤128	—	≥156

Interpretations of susceptible, intermediate, and resistant correlate zone size diameters with MIC values. A laboratory report of "susceptible" indicates that the suspected causative microorganism most likely will respond to therapy with carbenicillin. A laboratory report of "resistant" indicates that the infecting microorganism most likely will not respond to therapy. A laboratory report of "moderately susceptible" indicates that the microorganism is most likely susceptible if a high dosage of carbenicillin is used, or if the infection is such that high levels of carbenicillin may be attained as in urine. A report of "intermediate" using the disk diffusion method may be considered an equivocal result, and dilution tests may be indicated.

INDICATIONS AND USAGE

Geocillin (carbenicillin indanyl sodium) is indicated in the treatment of acute and chronic infections of the upper and lower urinary tract and in asymptomatic bacteriuria due to susceptible strains of the following organisms:

Escherichia coli
Proteus mirabilis
Morganella morganii (formerly *Proteus morganii*)
Providencia rettgeri (formerly *Proteus rettgeri*)
Proteus vulgaris
Pseudomonas
Enterobacter
Enterococci

Geocillin is also indicated in the treatment of prostatitis due to susceptible strains of the following organisms:

Escherichia coli
Enterococcus (*S. faecalis*)
Proteus mirabilis
Enterobacter sp.

WHEN HIGH AND RAPID BLOOD AND URINE LEVELS OF ANTIBIOTIC ARE INDICATED, THERAPY WITH GEOPEN (CARBENICILLIN DISODIUM) SHOULD BE INITIATED BY PARENTERAL ADMINISTRATION FOLLOWED, AT THE PHYSICIAN'S DISCRETION, BY ORAL THERAPY.

NOTE: Susceptibility testing should be performed prior to and during the course of therapy to detect the possible emergence of resistant organisms which may develop.

To reduce the development of drug-resistant bacteria and maintain effectiveness of Geocillin and other antibacterial drugs, Geocillin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Geocillin is ordinarily contraindicated in patients who have a known penicillin allergy.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on oral penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with a cephalosporin, and vice versa. Before initiating therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including GEOCILLIN(carbenicillin indanyl sodium), and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General: As with any penicillin preparation, an allergic response, including anaphylaxis, may occur particularly in a hypersensitive individual.

Long term use of Geocillin may result in the overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Since carbenicillin is primarily excreted by the kidney, patients with severe renal impairment (creatinine clearance of less than 10 ml/min) will not achieve therapeutic urine levels of carbenicillin.

In patients with creatinine clearance of 10–20 ml/min it may be necessary to adjust dosage to prevent accumulation of drug.

Prescribing Geocillin in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients: Patients should be counseled that antibacterial drugs including Geocillin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Geocillin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that

bacteria will develop resistance and will not be treatable by Geocillin or other antibacterial drugs in the future.

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

Laboratory Tests: As with other penicillins, periodic assessment of organ system function including renal, hepatic, and hematopoietic systems is recommended during prolonged therapy.

Drug Interactions: Geocillin (carbenicillin indanyl sodium) blood levels may be increased and prolonged by concurrent administration of probenecid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There are no long-term animal or human studies to evaluate carcinogenic potential. Rats fed 250–1000 mg/kg/day for 18 months developed mild liver pathology (e.g., bile duct hyperplasia) at all dose levels, but there was no evidence of drug-related neoplasia. Geocillin administered at daily doses ranging to 1000 mg/kg had no apparent effect on the fertility or reproductive performance of rats.

Pregnancy Category B: Reproduction studies have been performed at dose levels of 1000 or 500 mg/kg in rats, 200 mg/kg in mice, and at 500 mg/kg in monkeys with no harm to fetus due to Geocillin. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: It is not known whether the use of Geocillin in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Carbenicillin class antibiotics are excreted in milk although the amounts excreted are unknown; therefore, caution should be exercised if administered to a nursing woman.

Pediatric Use: Since only limited clinical data is available to date in children, the safety of Geocillin administration in this age group has not yet been established.

ADVERSE REACTIONS

The following adverse reactions have been reported as possibly related to Geocillin administration in controlled studies which include 344 patients receiving Geocillin.

Gastrointestinal: The most frequent adverse reactions associated with Geocillin therapy are related to the gastrointestinal tract. Nausea, bad taste, diarrhea, vomiting, flatulence, and glossitis were reported. Abdominal cramps, dry mouth, furry tongue, rectal bleeding, anorexia, and unspecified epigastric distress were rarely reported.

Dermatologic: Hypersensitivity reactions such as skin rash, urticaria, and less frequently pruritus.

Hematologic: As with other penicillins, anemia, thrombocytopenia, leukopenia, neutropenia, and eosinophilia have infrequently been observed. The clinical significance of these abnormalities is not known.

Miscellaneous: Other reactions rarely reported were hyperthermia, headache, itchy eyes, vaginitis, and loose stools.

Abnormalities of Hepatic Function Tests: Mild SGOT elevations have been observed following Geocillin administration.

OVERDOSAGE

Geocillin is generally nontoxic. Geocillin when taken in excessive amounts may produce mild gastrointestinal irritation. The drug is rapidly excreted in the urine and symptoms are transitory. The usual symptoms of anaphylaxis may occur in hypersensitive individuals.

Carbenicillin blood levels achievable with Geocillin are very low, and toxic reactions as a function of overdosage should not occur systematically. The oral LD_{50} in mice is 3,600 mg/kg, in rats 2,000 mg/kg, and in dogs is in excess of 500 mg/kg. The lethal human dose is not known.

Although never reported, the possibility of accumulation of indanyl should be considered when large amounts of Geocillin are ingested. Free indole, which is a phenol derivative, may be potentially toxic. In general 8–15 grams of phenol, and presumably a similar amount of indole, are required orally before toxicity (peripheral vascular collapse) may occur. The metabolic by-products of indole are nontoxic. In patients with hepatic failure it may be possible for unmetabolized indole to accumulate.

The metabolic by-products of Geocillin, indanyl sulfate and glucuronide, as well as free carbenicillin, are dialyzable.

DOSAGE AND ADMINISTRATION

Geocillin is available as a coated tablet to be administered orally.

Usual Adult Dose

URINARY TRACT INFECTIONS	
Escherichia coli, *Proteus* species, and *Enterobacter*	1–2 tablets 4 times daily
Pseudomonas and *Enterococcus*	2 tablets 4 times daily
PROSTATITIS	
Escherichia coli, Proteus mirabilis, Enterobacter and *Enterococcus*	2 tablets 4 times daily

HOW SUPPLIED

Geocillin is available as film-coated tablets in bottles of 100's (NDC 0049-1430-66). Each tablet contains carbenicillin indanyl sodium equivalent to 382 mg of carbenicillin.

Rx only

Distributed by

Roerig
Division of Pfizer Inc, NY, NY 10017

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