Adequate animal studies have not been conducted to determine the carcinogenic potential of probenecid or this drug combination. Since colchicine is an established mutagen, the ability to act as a carcinogen must be suspected and administration of probenecid and colchicine should involve a weighing of the benefit-to-risk when long-term administration is contemplated.

Drug Interactions
When probenecid is used to elevate plasma concentrations of penicillin, or other beta-lactams, or when such drugs are given to patients taking probenecid therapeutically, high plasma concentrations of the other drug may increase the incidence of adverse reactions associated with that drug. In the case of penicillin, or other beta-lactams, psychic disturbances have been reported.

The use of salicylates antagonizes the uricosuric action of probenecid (see WARNINGS). The uricosuric action of probenecid is also antagonized by probenecid.

Probenecid produces an insignificant increase in free sulfonamide plasma concentrations but a significant increase in total sulfonamide plasma levels. Since probenecid decreases the renal excretion of conjugated sulfonamides, plasma concentrations of the latter should be determined from time to time when a sulfonamide and probenecid and colchicine are coadministered for prolonged periods. Probenecid may prolong or enhance the action of oral sulfonfurazan and thereby increase the risk of hypoglycemia.

It has been reported that patients receiving probenecid require significantly less ethionamide for induction of anemia. In addition, hematoxylinic and topographie anemia were significantly prolonged in rats receiving probenecid. The coadministration of probenecid increases the mean plasma elimination half-life of a number of drugs which can lead to increased plasma concentrations. These include agents such as indomethacin, acetaminophen, naproxen, ketoprofen, meclofenamate, ibuprofen, and rifampin. Although the clinical significance of this observation has not been established, a lower dosage of the drug may be required to produce a therapeutic effect and increases in dosage of the drug in question should be made cautiously and in small increments when probenecid is being coadministered. Although specific instances of toxicity due to this possible interaction have not been observed to date, physicians should be alert to this possibility.

Probenecid given concomitantly with sulfinilamide had only a slight effect on plasma sulfide levels, while plasma levels of sulfonamide and sulfone were increased. Sulfinilamide was shown to produce a marked reduction in the uricosuric action of probenecid, which is probably not significant under most circumstances. In animals and in humans, probenecid has been reported to increase plasma concentrations of methotrexate (see WARNINGS).

False high readings for theophylline have been reported in an in vitro study, using the Schaeck and Waeter technique, when therapeutic concentrations of theophylline and probenecid were added to human plasma.

ADVERSE REACTIONS
The following adverse reactions have been observed and within each category are listed in order of decreasing severity.

Probenecid
Central Nervous System: headache, dizziness.
Metabolic: precipitation of acute gouty arthritis.
Gastrointestinal: hepatic necrosis, vomiting, nausea, anorexia, sore gums.
Musculoskeletal: nephritis, urethral and jaundice, renal colic, costovertebral pain, urinary frequency.
Hypersensitivity: anaphylaxis, fever, urticaria, pruritus.
Hematologic: aplastic anemia, leukopenia, hemorrhagic anemia.
Cardiovascular: myocardial infarction.
Integumentary: dermatitis, purpura, alopecia.
Allergic: anaphylactic reaction.
Colchicine
Side effects due to colchicine appear to be a function of dosage. The possibility of increased colchicine toxicity in the presence of hepatic dysfunction should be considered. The appearance of any of the following symptoms may require reduction of dosage or discontinuance of the drug:

Central Nervous System: peripheral neuritis.
Musculoskeletal: muscle weakness.
Gastrointestinal: nausea, vomiting, abdominal pain, or diarrhea may be particularly troublesome in the presence of peptic ulcer or peptic colon.
Hypersensitivity: urticaria.
Hematologic: aplastic anemia, agranulocytosis.
Integumentary: dermatitis, purpura, alopecia.
Allergic: anaphylactic reaction.
Toxic cases, colchicine may cause severe diarrhea, generalized vascular damage, and renal damage with hematuria and edema.

DOSEAGE AND ADMINISTRATION
Therapy with probenecid and colchicine should not be started until an acute gouty attack has subsided. However, if an acute attack is precipitated during therapy, probenecid and colchicine may be continued without changing the dosage, or additional colchicine or other appropriate therapy should be given to control the acute attack.

The recommended adult dosage is 1 tablet of probenecid and colchicine daily for one week, followed by 1 tablet twice a day thereafter.

Some degree of renal impairment may be present in patients with gout. A daily dosage of 2 tablets may be adequate. However, whenever necessary, the daily dosage may be increased by 1 tablet every second week until tolerance is obtained (usually not above 4 tablets per day), if symptoms of gouty arthritis are not controlled or if the 24-hour uric acid excretion is not above 700 mg. As noted, probenecid may not be effective in chronic renal insufficiency, particularly when the glomerular filtration rate is 30 ml/minute or less.

Gastric intolerance may be indicative of overdosage, and may be corrected by decreasing the dosage.

As uric acid tends to crystallize out of an acid urine, a liberal fluid intake is recommended, as well as sufficient sodium bicarbonate (0.5 to 0.75 g daily) to maintain an alkaline urine (see PRECAUTIONS).

Alkalization of the urine is recommended until the serum urate level returns to normal limits and topiphosphate deposits disappear, i.e., during the period when urinary excretion of uric acid is at a high level. Therapeutic, alkalinization of the urine and the usual restriction of purine-producing foods may be somewhat redundant.

Probenecid and colchicine (or probenecid) should be continued at the dosage that will maintain normal serum urate levels. When acute attacks have been absent for six months or more and serum urate levels remain within normal limits, the daily dosage of probenecid and colchicine may be decreased by 1 tablet every sixth month. The maintenance dosage should not be reduced to the point where serum urate levels tend to rise.

HOW SUPPLIED
Probenecid and Colchicine Tablets, USP 500 mg - 0.5 mg are blistered, white, capsule-shaped tablets coated with GL 250 on one side and supplied in bottles of 100, 500, and 1000.

Bottles of 100 (NDC 64980-149-01)
Bottles of 500 (NDC 64980-149-05)
Bottles of 1000 (NDC 64980-149-10)

Dispense in well-closed light resistant container with child-resistant closure.


To report SUSPECTED ADVERSE REACTIONS, contact Rising Pharmaceuticals at 1-266-361-8889 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Rx only

Manufactured by:
Rising Pharmaceuticals, Inc.
Minneapolis, MN 55401

Manufactured for:
Muir Pharmaceuticals, LLC.
Fairfield, NJ 07004

Rev. 10/11
DESCRIPTION
Probendol and colchicine contain probenecid, which is a carbonic anhydrase inhibitor, and colchicine, which has anti-gout activity, the mechanism of which is unknown.
Probeneid is the generic name for 4- (dipropargyloxiranio) sulfonil benzoic acid. The structural formula is represented below.

Probeneid is a white or nearly white, finely crystalline powder.

It is soluble in dilute alcohol, in chloroform, and in acetone; it is practically insoluble in water and in dilute acids.

Colchicine is an alkaloid obtained from various species of Colchicum. The chemical name for colchicine is (5S)-5,6,7,9-tetrahydro-7-oxo-1,2,3,10-tetrahydrobenzene-9-oxide (chelirubine-9-yl) acetate. The structural formula is represented below.

Colchicine consists of pale yellow scales or powder; it darkens on exposure to light. Colchicine is soluble in water, freely soluble in alcohol and in chloroform, and slightly soluble in ether.

Each tablet for oral administration contains 500 mg of probenecid and 0.5 mg of colchicine. Each tablet also contains the following inactive ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate and sodium starch glycolate.

CLINICAL PHARMACOLOGY
Probeneid is a uricosuric and renal tubular blocking agent. It inhibits the tubular reabsorption of urate, thus increasing the urinary excretion of uric acid and decreasing serum urate levels. Effective uricosuria reduces the incidence of gouty attacks, retards urate deposition, and promotes reabsorption of urate deposits.

Probeneid inhibits the tubular secretion of penicillin and usually increases penicillin plasma levels by a factor of the antibiotic is given. A 2-fold to 4-fold elevation has been demonstrated for various penicillins.

Probeneid also has been reported to inhibit the renal transport of many other compounds including amphotericin B (AMBR), amoxicillin (amoxicillin acetate, PAS), chlorothiazide, chlorothiazide and related substituted organic acids, 17-ketosteroids, pantothenic acid, phenylbutazone (PBA), sulfonamides, and sulfonanilides. See also Drug Interactions.

Probeneid decreases both hepatic and renal excretion of sulfobromophthalein (SBP). The tubular reabsorption of sulfobromophthalein is inhibited in hyperuricemia but not in hyperuricemia individuals.

Probeneid does not influence plasma concentrations of salicylates, nor the excretion of streptomycin, chloramphenicol, chlorotetracycline, or neomycin.

The mode of action of colchicine in gout is unknown. It is not an analgesic, though it relieves pain in acute attacks of gout.
It is not an uricosuric agent and will not prevent progression of gout to chronic gouty arthritis. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute attacks and to relieve the residual pain and mild discomfort that patients with gout occasionally feel.

In man and certain other animals, colchicine can produce a temporary leukopenia that is followed by leukocytosis. Colchicine has other pharmacologic activities in animals. It alters neuromuscular function, intensifies gastrointestinal activity by neurogenic stimulation, increases sensitivity to central depressants, increases response to sympathomimetic compounds, depresses the respiratory center, constricts blood vessels, causes hypertension by central vasoconstriction, and lowers body temperature.

INDICATIONS AND USAGE
For the treatment of chronic gouty arthritis when concomitantly treated with frequent, recurrent acute attacks of gout.

CONTRAINDICATIONS
Hypersensitivity to the product or to probenecid or colchicine.
Probeneid and colchicine tablets are contraindicated in children under 2 years of age.
Not recommended in persons with known blood dyscrasias or urea acid stones.

Therapy with probenecid and colchicine should not be started until an acute gouty attack has subsided.

Pregnancy:
Probeneid is an uricosuric and renal tubular blocking agent. It inhibits the tubular secretion of penicillin and usually increases penicillin plasma levels by a factor of the antibiotic is given. A 2-fold to 4-fold elevation has been demonstrated for various penicillins.

Probeneid also has been reported to inhibit the renal transport of many other compounds including amphotericin B (AMBR), amoxicillin (amoxicillin acetate, PAS), chlorothiazide, chlorothiazide and related substituted organic acids, 17-ketosteroids, pantothenic acid, phenylbutazone (PBA), sulfonamides, and sulfonanilides. See also Drug Interactions.
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Pregnancy:
Probeneid crosses the placental barrier and appears in cord blood. Colchicine can pass cell division in animals and plants. In certain species of animals under certain conditions, colchicine has protracted mitogenic effects. The possibility of such effects in humans also has been reported. Because of the colchicine component, probenecid and colchicine is contraindicated in pregnant patients. The use of any drug in women of childbearing potential requires that the anticipated benefit be weighed against the possible hazards.

WARNINGS
Exacerbation of gout following therapy with probenecid and colchicine may occur; in such cases additional colchicine or other appropriate therapy is advisable.

Probeneid increases plasma concentrations of methotrexate in both animals and humans. In animal studies, increased methotrexate toxicity has been reported. If probenecid and colchicine is given with methotrexate, the dosage of methotrexate should be reduced and serum levels may need to be monitored.

In patients on probenecid and colchicine the use of salicylates in smaller or larger doses is contraindicated because it antagonizes the uricosuric action of probenecid. If the hepatic action of salicylates in the renal tubules accounts for the so-called "paradoxical effect" of uricosuric agents, in patients on probenecid and colchicine who require a mild analgesic agent the use of acetylsalicylic acid or aspirin, rather than small doses of salicylates would be preferred.

Rarely, severe allergic reactions and anaphylaxis have been reported with the use of probenecid and colchicine. Most of these have been reported to occur within several hours after readministration following prior use of the drug. The appearance of hypersensitivity reactions requires cessation of therapy with probenecid and colchicine.

Colchicine has been reported to adversely affect spermatogenesis in animals. Reversible azoospermia has been reported in one patient.

PRECAUTIONS
General
Hematuria, renal colic, costovertebral pain, and formation of uric acid stones associated with use of probenecid and colchicine in gouty patients may be prevented by alkalization of the urine and a liberal fluid intake (see DOSEs AND ADMINISTRATION). In cases when prkell is administered, the acid-base balance of the patient should be watched.

Use with caution in patients with a history of peptic ulcer.

Probeneid and colchicine has been used in patients with some renal impairment but dosage requirements may be increased. Probeneid and colchicine may not be effective in chronic renal insufficiency particularly when the glomerular filtration rate is 30 ml/minute or less.

A reducing substance may appear in the urine of patients receiving probenecid. This disappears with discontinuance of therapy. Suspected glycosuria should be confirmed by using a test specific for glucose.