PROBENECID 500 mg
with COLCHICINE 0.5 mg
TABLETS

DESCRIPTION
Probencid is the generic name for p-(dipropylamino)benzoic acid. Colchicine is an alkaloid obtained from various species of Colchicum.

ACTIONS
Probencid 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 uric acid levels. Effective uricosuria reduces the mobile urate pool, retards urate deposition, and promotes resorption of urate deposits. Probencid inhibits the tubular secretion of penicillin and usually increases penicillin plasma levels by any route the antibiotic is given. A 2-fold to 4-fold elevation has been demonstrated for various penicillins.

Probencid also decreases the urinary excretion of aminosalicylic acid (PAS), aminophenylacetic acid (PAA), phenylbutazone (PBP), sodium salicylate (SAS), and sodium isosorbide dinitrate. It decreases both hepatic and renal excretion of sulfobromophthalain (BSP). The tubular reabsorption of phosphorus is inhibited in hyperparathyroid but not in hypoparathyroid individuals.

Probencid produces an insignificant increase in free sufa plasma concentrations but a significant increase in total sufa plasma levels. Probencid also produces a significant increase in indomethacin plasma levels.

Probencid does not influence plasma concentrations of salicylates, nor the excretion of streptomycin, chloramphenicol, chloramphenicol, oxytetracycline, 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 a 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 actions in animals: It alters neuromuscular function, intensifies gastrointestinal activity by neurogenic stimulation, increases sensitivity to certain depressants, heightens response to sympathomimetic compounds, depresses the respiratory center, constricts blood vessels, causes hypertension by central vasomotor stimulation, and lowers body temperature.

INDICATIONS
For the treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout.

CONTRAINDICATIONS
Hypersensitivity to probenecid or colchicine. Not recommended in persons with known blood dyscrasies or uric acid kidney stones. Therapy with Probenecid and Colchicine should not be started until an acute gouty attack has subsided.
WARNINGS
Exacerbation of gout following therapy with probenecid and colchicine may occur; in such cases additional colchicine therapy is advisable.

In patients on probenecid and colchicine the use of salicylates in either small or large doses is contraindicated because it antagonizes the uricosuric action of probenecid. The toxic effects of salicylates in the renal tubules account for the so-called 'paradoxic effect' of uricosuric agents. In patients on probenecid and colchicine who require a mild analgesic agent the use of acetaminophen rather than small doses of salicylates would be preferred.

The appearance of hypersensitivity reactions require cessation of therapy with probenecid and colchicine. Cell division in animals and plants can be arrested by colchicine. In certain species of animal under certain conditions it has produced teratogenic effects and has adversely affected spermatogenesis. Reversible azoospermia has been reported in one patient.

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

Use with caution in patients with a history of peptic ulcer. Probenecid and colchicine have been used in patients with some renal impairment but dosage requirements may be increased. Probenecid and colchicine may be ineffective in chronic renal insufficiency particularly when the glomerular filtration rate is 30 ml/min or less.

As 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.

A buffered substance may appear in the urine of patients receiving probenecid. Although this disappears without discontinuation of therapy, a false diagnosis of gout may be made because of a false-positive Benedict's test.

ADVERSE REACTIONS
Headache, gastrointestinal symptoms (e.g., nausea, vomiting), abdominal frequency, hypersensitivity reactions (including anaphylaxis, dermatitis, pruritus, and fever), sore gums, flushing, dizziness, and anemia have occurred following the use of probenecid; also hemolytic anemia which in some instances could be related to genetic deficiency of glucose-6-phosphate dehydrogenase in red blood cells. Nephrotic syndrome, hepatic necrosis, and aplastic anemia occur rarely.

Side effects due to colchicine appear to be a function of dosage. The most prominent symptoms are referable to the gastrointestinal tract (e.g., nausea, vomiting, abdominal pain, diarrhea) and may be particularly troublesome in the presence of peptic ulcer or spastic colon. At toxic doses colchicine may cause severe diarrhea, generalized vascular damage, and renal damage with hematuria and oliguria. Muscular weakness, which disappears with discontinuation of the drug, may occur. Urticaria, dermatitis, and purpura have also been reported. Hypersensitivity to colchicine is a rare occurrence, but should be borne in mind. The appearance of any of the aforementioned symptoms may require reduction of dosage or discontinuation of the drug. When given for prolonged periods, colchicine may cause agranulocytosis, aplastic anemia, and peripheral neuritis. Loss of hair attributable to colchicine therapy has been reported.

Possibility of increased colchicine toxicity in the presence of hepatic dysfunction should be considered.

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, and additional colchicine should be given to control the acute attack.

The recommended adult dosage is 1 Probenecid and Colchicine tablets daily for 1 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, if necessary the daily dosage may be increased by 1 tablet every 4 weeks within tolerance (and usually not above 4 tablets per day) if symptoms of gouty arthritis are not controlled or if the 24 hour urate excretion is still above 100 mg.

As noted, probenecid may not be effective in chronic renal insufficiency particularly when the glomerular filtration rate is 30 ml/min or less.

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

As urate and endogenous loss of an acid urine, a liberal fluid intake is recommended as well as sufficient sodium bicarbonate (3 to 7.5 g daily) or potassium citrate (7.5 g daily) to maintain an alkaline urine (see PRECAUTIONS).

Alkalization of the urine is recommended until the serum uric acid level returns to normal limits (maximum normal levels in males about 6 mg per 100 ml in females about 5 mg per 100 ml) and uric acid and urate excretion are at a high level. When symptoms are well controlled, the period of purine-producing foods may be somewhat relaxed.

Probenecid and Colchicine (or Probenecid) should be continued at the dosage that will maintain normal serum uric acid levels. When acute attacks have been absent for six months or more serum uric acid levels remain within normal limits, the daily dosage of Probenecid and Colchicine may be decreased by 1 tablet every 6 months. The maintenance dosage should not be reduced to the point where serum uric acid levels tend to rise.

HOW SUPPLIED
Probenecid 300 mg with Colchicine 0.5 mg Tablets (Product No. 3361) are supplied in bottles of 1 000 and Unit-of-Issue 100's with CRC.

Manufactured to the specifications of LEDELER LABORATORIES DIVISION American Cyanamid Company, Pearl River, N.Y. 10965
by DANBURY PHARMACAL, INC. Danbury, Conn. 06810

REV. 12/77
PROBENCID with COLCHICINE TABLETS

Each tablet contains:
Probencid 500 mg
Colchicine 0.5 mg

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured to the specifications of LEDERLE LABORATORIES DIVISION American Cyanamid Company, Pearl River, N.Y. 10965

By DANBURY PHARMACAL, INC., Danbury, Conn. 06810

For Your Information and File
THIS FACSIMILE OF TEXT IS THE LATEST PRINTING

Probenecid with Colchicine Tablets

EACH TABLET CONTAINS:
Probenecid 500 mg
Colchicine 0.5 mg

CAUTION:
Federal law prohibits dispensing without prescription.

DOSAGE:
For complete directions for use, see accompanying circular.

1000 TABLETS

Probenecid with Colchicine Tablets

This package not for household dispensing. Preserve in well-closed, light-resistant containers.

Control No. Exp. Date

Manufactured to the specifications of LIEDEL LABORATORIES DIVISION American Cyanamid Company, Pearl River, New York
by DANBURY PHARMACAL, INC., Danbury, Conn. 06810

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