CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

86954

DRAFT FINAL PRINTED LABELING

82622
02

PROBENECID 500 mg with COLCHICINE 0.5 mg TABLETS

APPROVED

SEP 6 1979

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

ACTIONS
Probenecid 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 miscible urate pool, retards urate deposition, and promotes resorption of urate deposits. Probenecid 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.

Probenecid also decreases the urinary excretion of aminosalicylic acid (PAS), aminohippuric acid (PAH), phenolsulfonphthalein (PSP), pantothenic acid, 17-ketosteroids, and sodium iodomethamate. It decreases both hepatic and renal excretion of sulfobromophthalein (BSP). The tubular reabsorption of phosphorus is inhibited in hypoparathyroid but not in euparathyroid individuals. Probenecid produces an insignificant increase in free sulfa plasma concentrations but a significant increase in total sulfa plasma levels. Probenecid also produces a significant increase in indomethacin plasma levels.

Probenecid does not influence plasma concentrations of salicylates, nor the excretion of streptomycin, chloramphenicol, chlortetracycline, 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 central 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 dyscrasias 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 biphasic 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 acetominophen 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 alkalization of the urine and a liberal fluid intake (see DOSAGE AND ADMINISTRATION). In these cases when alkali 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 has been used in patients with some renal impairment but dosage requirements may be increased. Probenecid and colchicine may not be effective in chronic renal insufficiency particularly when the glomerular filtration rate is 30 ml/min. or less.

As probenecid decreases the renal excretion of conjugated sulfa drugs, plasma concentrations of the latter should be determined from time to time when a sulfa drug and probenecid and colchicine are coadministered for prolonged periods.

A reducing substance may appear in the urine of patients receiving probenecid. Although this disappears with discontinuance of therapy, a false diagnosis of glycosuria may be made because of a false-positive Benedict's test.

ADVERSE REACTIONS

Headache, gastrointestinal symptoms (e.g., anorexia, nausea, vomiting), urinary 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 referrable 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 discontinuance of therapy, urticaria, dermatitis, and purpura have also been reported. Hypersensitivity to colchicine is a very rare occurrence, but should be borne in mind. The appearance of any of the aforementioned symptoms may require reduction of dosage or discontinuance 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. The possibility of increased colchicine toxicity in the presence of hepatic dysfunction should be considered.

DOSAGE 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 tablet 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, if necessary the daily dosage may be increased by 1 tablet every four weeks within tolerance (and usually not above 4 tablets per day) if symptoms of gouty arthritis are not controlled or the 24 hour urate 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/min. or less.

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

As urates tend to crystallize out 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 level in males about 8 mg per 100 ml, in females about 5 mg per 100 ml) and tophaceous deposits disappear, i.e., during the period when urinary excretion of urates is at a high level. Thereafter, alkalization of the urine and the usual restriction 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 and serum uric acid levels remain within normal limits, the daily dosage of Probenecid and Colchicine may be decreased by 1 tablet every six months. The maintenance dosage should not be reduced to the point where serum uric acid levels tend to rise.

HOW SUPPLIED

Probenecid 500 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
LEDERLE LABORATORIES DIVISION
American Cyanamid Company,
Pearl River, N.Y. 10965
by
DANBURY PHARMACAL, INC.
Danbury, Conn. 06810

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PROBENECID with COLCHICINE TABLETS LEDERLE

NDC 0005-3361-62
Control No.
Do not use after

PROBENECID with COLCHICINE TABLETS LEDERLE

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.

Preserve in well-closed, light-resistant containers.

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

_____ Tint Size

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Box or Jar _____

Grain Direction _____

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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

Dr.

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
LEDERLE LABORATORIES DIVISION
American Cyanamid Company,
Pearl River, N.Y. 10965
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Danbury, Conn. 06810

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