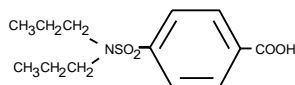


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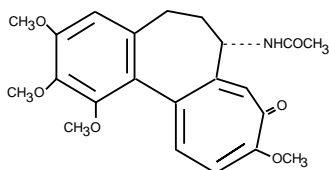
**PROBENECID AND
COLCHICINE TABLETS USP
Rx only**

DESCRIPTION

Probenecid-Colchicine, contains probenecid, which is a uricosuric agent, and colchicine, which has anti-gout activity, the mechanism of which is unknown. Probenecid is the generic name for 4-[(dipropylamino)sulfonyl] benzoic acid (molecular weight 285.36). It has the following structural formula:



Probenecid is a white or nearly white, fine, crystalline powder. It is soluble in dilute alkali, in 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 (S)-N-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo [a] heptalen-7-yl) acetamide (molecular weight 399.43). It has the following structural formula:



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 contains 500 mg of probenecid and 0.5 mg colchicine and the following inactive ingredients: colloidal silicon dioxide, corn starch, magnesium stearate, povidone, pregelatinized starch, sodium starch glycolate, stearic acid.

CLINICAL PHARMACOLOGY

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 urate 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 has been reported to inhibit the renal transport of many other compounds including aminohippuric acid (PAH), aminosalicilic acid (PAS), indomethacin, sodium iodomethamate and related iodinated organic acids, 17-ketosteroids, pantothenic acid, phenolsulfonphthalein (PSP), sulfonamides, and sulfonyleureas (See also **PRECAUTIONS, Drug Interactions**).

Probenecid decreases both hepatic and renal excretion of sulfobromophthalein (BSP). The tubular reabsorption of phosphorus is inhibited in hypoparathyroid but not in euparathyroid individuals.

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 AND USAGE

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

CONTRAINDICATIONS

Hypersensitivity to this product or to probenecid or colchicine.

Children under 2 years of age.

Not recommended in persons with known blood dyscrasias or uric acid kidney stones.

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

Pregnancy: Probenecid crosses the placental barrier and appears in cord blood. Colchicine can arrest cell division in animals and plants. In certain species of animals under certain conditions, colchicine has produced teratogenic effects. The possibility of such effects in humans also has been reported. Because of the colchicine component, probenecid-colchicine is contraindicated in pregnant patients. The use of any drug in women of childbearing potential requires that the anticipated benefit be weighed against possible hazards.

WARNINGS

Exacerbation of gout following therapy with probenecid-colchicine may occur; in such cases additional colchicine or other appropriate therapy is advisable. Probenecid increases plasma concentrations of methotrexate in both animals and humans. In animal studies, increased methotrexate toxicity has been reported. If probenecid-colchicine is given with methotrexate, the dosage of methotrexate should be reduced and serum levels may need to be monitored.

In patients on probenecid-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-colchicine who require a mild analgesic agent the use of acetaminophen rather than small doses of salicylates would be preferred.

Rarely, severe allergic reactions and anaphylaxis have been reported with the use of probenecid-colchicine. Most of these have been reported to occur within several hours after readministration following prior usage of the drug.

The appearance of hypersensitivity reactions requires cessation of therapy with probenecid-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 the use of probenecid-colchicine in gouty patients may be prevented by alkalinization 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-colchicine has been used in patients with some renal impairment but dosage requirements may be increased. Probenecid-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 dis-

appears with discontinuance of therapy. Suspected glycosuria should be confirmed by using a test specific for glucose.

Adequate animal studies have not been conducted to determine the carcinogenicity potential of probenecid or this drug combination. Since colchicine is an established mutagen, its ability to act as a carcinogen must be suspected and administration of probenecid-colchicine should involve a weighing of the benefit-vs-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 pyrazinamide. 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-colchicine are coadministered for prolonged periods. Probenecid may prolong or enhance the action of oral sulfonylureas and thereby increase the risk of hypoglycemia.

It has been reported that patients receiving probenecid require significantly less thiopental for induction of anesthesia. In addition, ketamine and thiopental anesthesia were significantly prolonged in rats receiving probenecid.

The concomitant administration 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, lorazepam, 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 co-administered. Although specific instances of toxicity due to this potential interaction have not been observed to date, physicians should be alert to this possibility.

Probenecid given concomitantly with sulindac had only a slight effect on plasma sulfide levels, while plasma levels of sulindac and sulfone were increased. Sulindac was shown to produce a modest reduction in the uricosuric action of probenecid, which probably is not significant under most circumstances.

In animals and in humans, probenecid has been reported to increase plasma concentrations of methotrexate (see **WARNINGS**).

Falsely high readings for theophylline have been reported in an *in vitro* study, using the Schack and Waxler technic, 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.

Genitourinary: nephrotic syndrome, uric acid stones with or without hematuria, renal colic, costovertebral pain, urinary frequency.

Hypersensitivity: anaphylaxis, fever, urticaria, pruritus.

Hematologic: aplastic anemia, leukopenia, hemolytic anemia which in some patients could be related to genetic deficiency of glucose -6- phosphate dehydrogenase in red blood cells, anemia.

Integumentary: dermatitis, alopecia, flushing.

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: muscular weakness.

Gastrointestinal: nausea, vomiting, abdominal pain, or diarrhea may be particularly troublesome in the presence of peptic ulcer or spastic colon.

Hypersensitivity: urticaria.

Hematologic: aplastic anemia, agranulocytosis.

Integumentary: dermatitis, purpura, alopecia.

At toxic doses, colchicine may cause severe diarrhea, generalized vascular damage, and renal damage with hematuria and oliguria.

DOSAGE AND ADMINISTRATION

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

The recommended adult dosage is 1 tablet of probenecid-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, 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 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 (3 to 7.5 g daily) or potassium citrate (7.5 g daily) to maintain an alkaline urine (see **PRECAUTIONS**).

Alkalinization of the urine is recommended until the serum urate level returns to normal limits and tophaceous deposits disappear, i.e., during the period when urinary excretion of uric acid is at a high level. Thereafter, alkalinization of the urine and the usual restriction of purine-producing foods may be somewhat relaxed. Probenecid-colchicine 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-colchicine may be decreased by 1 tablet every six months. The maintenance dosage should not be reduced to the point where serum urate levels tend to rise.

HOW SUPPLIED

Probenecid and Colchicine Tablets USP are available as 500 mg/0.5 mg, capsule shaped, scored, white tablets debossed with company logo and 2193 on one side packaged in bottles of 100 and 1000 tablets.

PHARMACIST: Dispense in a well-closed, light-resistant container as defined in the USP. Use child-resistant closure (as required).

Store at controlled room temperature 15°-30°C (59°-86°F)(See USP).

MANUFACTURED BY
IVAX PHARMACEUTICALS, INC.
MIAMI, FL 33137

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