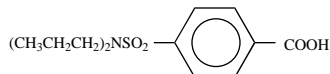


DRUGS-ABOUT.COM**PROBENECID
TABLETS USP
Rx only****DESCRIPTION**

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

Probenecid is available as 500 mg tablets for oral administration and contains the following inactive ingredients: colloidal silicon dioxide; colorants: D&C Yellow No. 10, FD&C Yellow No. 6, titanium dioxide; corn starch, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone, sodium starch glycolate, stearic acid.

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 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), aminosalicic acid (PAS), dyphylline, indomethacin, sodium iodomethamate and related iodinated organic acids, 17-ketosteroids, pantothenic acid, phenol-sulfonphthalein (PSP), sulfonamides, and sulfonyleureas. (see also **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.

INDICATIONS

For treatment of hyperuricemia associated with gout and gouty arthritis.

As an adjunctive to therapy with penicillin, or with ampicillin, methicillin, oxacillin, cloxacillin, or nafcillin, for elevation and prolongation of plasma levels by whatever route the antibiotic is given.

CONTRAINDICATIONS

Hypersensitivity to probenecid. Children under 2 years of age.

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

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

WARNINGS

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

Probenecid should not be given to patients receiving therapy with methotrexate since in animal studies probenecid has been reported to increase methotrexate plasma levels with resultant increased methotrexate toxicity.

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

The appearance of hypersensitivity reactions requires cessation of therapy with probenecid.

PRECAUTIONS

Hematuria, renal colic, costovertebral pain, and formation of uric acid stones associated with the use of probenecid in gouty patients may be prevented by alkalization of the urine and 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 has been used in patients with some renal impairment, but dosage requirements may be increased. Probenecid may not be effective in chronic renal insufficiency particularly when the glomerular filtration rate is 30 mL/minute or less. Because of its mechanism of action, probenecid is not recommended in conjunction with a penicillin in the presence of known renal impairment.

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.

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.

In gouty patients, exacerbation of gout and uric acid stones with or without hematuria, renal colic, or costovertebral pain, have been observed. Nephrotic syndrome, hepatic necrosis, and aplastic anemia occur rarely. Hemolytic anemia, which in some instances could be related to genetic deficiency of glucose-6-phosphate dehydrogenase in red blood cells, has been reported.

DRUG INTERACTIONS

The use of salicylates antagonizes the uricosuric action of probenecid (see **WARNINGS**).

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 are coadministered for prolonged periods. Probenecid may prolong or enhance the action of oral sulfonyleureas and thereby increase the risk of hypoglycemia.

When probenecid is given to patients receiving indomethacin, the plasma levels of indomethacin are likely to be increased. Therefore, a lower dosage of indomethacin may be required to produce a therapeutic effect, and increases in the dosage of indomethacin should be made cautiously and in small increments. Probenecid may increase plasma levels of rifampin. The clinical significance of this is not known.

Probenecid when given concomitantly with dyphylline, which is excreted unchanged by the kidneys, inhibits dyphylline excretion. This inhibition has been shown to prolong the half-life of dyphylline significantly which has to be taken into consideration when administering this drug. In animals, probenecid has been reported to increase plasma concentrations of methotrexate with resultant increase in toxicity of the antineoplastic agent (see **WARNINGS**).

Falsely high readings for theophylline have been reported in an *in vitro* study, using the Schack and Waxler technique, when therapeutic concentrations of theophylline and probenecid were added to human plasma.

DOSAGE AND ADMINISTRATION

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

The recommended adult dosage is 250 mg (1/2 probenecid tablet), twice a day for one week, followed by 500 mg (1 tablet) twice a day thereafter.

Some degree of renal impairment may be present in patients with gout. A daily dosage of 1000 mg may be adequate. However, if necessary, the daily dosage may be increased by 500 mg increments, every 4 weeks within tolerance (and usually not above 2000 mg per day) if symptoms of gouty arthritis are not controlled or the 24 hour urate excretion is not above 700 mg. 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 (3000 to 7500 mg daily), or potassium citrate (7500 mg 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, alkalization of the urine and the usual restriction of purine-producing goods may be somewhat relaxed. Probenecid should be continued at the dosage that will maintain normal serum urate levels. When acute attacks have been absent for 6 months or more and serum urate levels remain within normal limits, the daily dosage may be decreased by 500 mg every 6 months. The maintenance dosage should not be reduced to the point where serum urate levels tend to rise.

Probenecid and Penicillin Therapy (General):

Adults: The recommended dosage is 2000 mg (4 tablets of probenecid) daily in divided doses. This dosage should be reduced in older patients in whom renal impairment may be present.

Children: 2-14 years of age:
Initial Dose: 25 mg/kg body weight (or 0.7 g/square meter body surface).
Maintenance Dose: 40 mg/kg body weight (or 1.2 g/square meter body surface) per day, divided into 4 doses.
 For children weighing more than 50 kg (110 pounds) the adult dosage is recommended. Probenecid is contraindicated in children under 2 years of age. The PSP excretion test may be used to determine the effectiveness of probenecid in retarding penicillin excretion and maintaining therapeutic levels. The renal clearance of PSP is reduced to about one-fifth the normal rate when dosage of probenecid is adequate.

Penicillin Therapy (Gonorrhea):
 SEE TABLE BELOW

PROBENECID PENICILLIN THERAPY (GONORRHEA)*

STATEMENT	RECOMMENDED REGIMENS**	REMARKS
Uncomplicated gonococcal infection in men and women urethral, cervical, rectal	4.8 million units of aqueous procaine penicillin G+ I.M., in at least 2 doses injected at different sites at one visit + 1 g of probenecid orally just before injections or 3.5 g of ampicillin+ orally + 1 g of probenecid orally given simultaneously.	Follow Up: Obtain urethral and other appropriate cultures from men, and cervical, anal, and other appropriate cultures from women, 7 to 14 days after completion of treatment. Treatment of sexual partners. Persons with known recent exposure to gonorrhea should receive same treatment as those known to have gonorrhea. Examination and treatment of male sex partners of persons with gonorrhea are essential because of high prevalence of non-symptomatic urethral gonococcal infection in such men.
Pharyngeal gonococcal infection in men and women	4.8 million units of aqueous procaine penicillin G+ I.M., in at least 2 doses injected at different sites at one visit + 1 g of probenecid just before injections.	Pharyngeal gonococcal infections may be more difficult to treat than anogenital gonorrhea. Post-treatment cultures are essential.
Uncomplicated gonorrhea in pregnant patients	4.8 million units of aqueous procaine penicillin G+ I.M., in at least 2 doses injected at different sites at one visit or 3.5 g of ampicillin+ orally + 1 g of probenecid orally given simultaneously	
Acute gonococcal salpingitis	Outpatients: Aqueous procaine penicillin G+ or ampicillin+ with probenecid as for gonorrhea in pregnancy, followed by 500 mg of ampicillin+ 4 times a day for 10 days Hospitalized patients: See details in CDC recommendations	Follow up of patients with acute salpingitis is essential. All patients should receive repeat pelvic examinations and cultures for <i>Neisseria gonorrhoeae</i> after treatment. Examination and appropriate treatment of male sex partners are essential because of high prevalence of non-symptomatic urethral gonorrhea in such men.

Disseminated gonococcal infection(arthritis-dematitis syndrome)	10 million units of aqueous crystalline penicillin G+ I.V. a day for 3 days or until significant clinical improvement occurs. May be followed with 500 mg of ampicillin+ 4 times a day orally to complete 7 days of treatment or 3.5 g of ampicillin+ orally with 1 g of probenecid followed by 500 mg of ampicillin+ 4 times a day for at least 7 days	
Gonococcal infection in children	For postpubertal children and/or those weighing over 45 kg. (100 lb.) use the dosage regimens given above for adults Uncomplicated vulvovaginitis and urethritis: aqueous procaine penicillin G+ 75,000-100,000 units/kg I.M. with probenecid 23 mg/kg orally	See CDC recommendations for detailed information about prevention and treatment of neonatal gonococcal infection and gonococcal ophthalmia.

NOTE: Before treating gonococcal infections in patients with suspected primary to secondary syphilis, perform proper diagnostic procedures including darkfield examinations. If concomitant syphilis is suspected, perform monthly serological tests for at least 4 months.

*Recommended by Venereal Disease Control Advisory Committee, Center for Disease Control, U.S. Department of Health, Education, and Welfare, Public Health Service (Morbidity and Mortality Weekly Report, Vol. 23:341, 342, 347, 348, October 11, 1974).

**See CDC recommendations for definition of regimens of choice, alternative regimens, treatment of hypersensitive patients, and other aspects of therapy.

+See package circulars of manufacturers for detailed information about contraindications, warnings, precautions, and adverse reactions.

HOW SUPPLIED

Probenecid tablets USP are available as yellow, film-coated, capsule shaped, bisected tablets, debossed with company logo and 2190, containing 500 mg probenecid, USP packaged in bottles of 100 and 1000 tablets.
 PHARMACIST: Dispense in a well-closed container as defined in the USP. Use child-resistant closure.
 Store at controlled room temperature 15°-30°C (59°-86°F) (See USP).

MANUFACTURED BY
 IVAX PHARMACEUTICALS, INC.
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