**Probenecid-AFT**  
*Probenecid 500 mg Tablets*

**Presentation**
Probenecid-AFT tablets are yellow capsule-shaped, film coated tablets, bisected on one side and plain on the other. Each tablet contains 500 mg Probenecid. This product is not able to deliver all approved dose regimes.

**Uses**

**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. Despite pronounced uricosuric activity, time is required to achieve clinical results. Acute attacks of gout may occur during the early phase of therapy in spite of the return to normal of the serum uric acid level. However, with continued use for some months, attacks of acute gout become less frequent and less intense. As urate deposits in periarticular and articular structures are reabsorbed, joint pain is relieved, greater articular mobility is achieved, and further joint destruction may be averted. As urate deposits are mobilised from the gouty kidney, renal function may improve and further destructive changes may be prevented. Probenecid inhibits the tubular reabsorption of phosphorus in hypoparathyroid but not in europarathyroid individuals.

**Pharmacokinetics**

**Absorption**
Probenecid is completely absorbed after oral administration. Peak plasma levels are reached in two to four hours.

**Distribution**
Between 85 and 95% of probenecid is bound to plasma albumin; the apparent volume of distribution of the drug is 11 litres.

**Metabolism**
Metabolism involves oxidation of alkyl side chains and glucuronide conjugation. The major metabolite, probenecid acyl glucuronide, accounts for close to 50% of the dose. Approximately equal amounts (10 - 15%) of mono-n-propyl, secondary alcohol and carboxylic acid metabolites are excreted. The primary alcohol metabolite is not found in measurable amounts. The plasma half-life is between six and twelve hours, and increases with increasing dose (over the therapeutic dosage range) due to non-linear disposition.

**Elimination**
Probenecid is excreted both by glomerular filtration (unbound fraction only) and by active secretion by the proximal renal tubule. Following oral administration, 75 - 88% of the dose is found in the urine mainly as metabolites and as lesser amounts of unchanged drug. The urinary excretion of unchanged probenecid is dependent on both the pH and flow rate of urine.

**Indications**

**Gout**
Probenecid is a uricosuric agent for the treatment of hyperuricaemia in all stages of gout and gouty arthritis except a presenting acute attack. Asymptomatic hyperuricaemia seems to occur in a significant percentage of relatives of gouty patients. Probenecid may be given prophylactically to these people to forestall gouty attacks and urate deposition in tissues.
By virtue of its effective uricosuric activity, probenecid may be used to control the hyperuricaemia induced or aggravated by many diuretics employed for the treatment of oedema and hypertension (e.g. thiazides and similar diuretics).

**B-Lactam Antibiotic Therapy**

Probenecid is indicated for the elevation and prolongation of plasma levels by whatever route the antibiotic is given. A two-to-fourfold increase in plasma levels has been demonstrated for penicillin G or V, the synthetic penicillins, ampicillin, methicillin, oxacillin, cloxacillin, nafcillin, carbenicillin, and for the cephamycins, cefoxitin sodium, and the cephalosporins, cephalothin, cephalaxin and cephaloglycin.

**Dosage and Administration**

**Gout**

Probenecid therapy should not be initiated until an acute gouty attack has subsided. Should an acute attack be precipitated during therapy, the drug may be continued without changing the dosage, and therapeutic doses of colchicine, indomethacin, or other appropriate therapy may be administered to control the acute attack.

**Adult**

The recommended dose for adults is 250 mg (½ tablet) twice a day for one week, followed by 500 mg (1 tablet) twice a day thereafter. As some degree of renal impairment is common in patients with gout, a daily dosage of 1000 mg may be adequate for many patients. The daily dosage may be increased, if necessary, by increments of 500 mg every four weeks, but usually not beyond 2000 mg daily, if symptoms of gouty arthritis are not controlled or the 24-hour urate excretion is not above 700 mg. In chronic renal insufficiency particularly when the glomerular filtration rate is 30 mL/minute or less probenecid may not be effective. Gastric intolerance may be indicative of overdosage. This may be corrected by reducing the dose without losing the required therapeutic response. Probenecid should be continued at a dosage that will maintain a normal serum uric acid level. When acute attacks have been absent for six months or more and serum uric acid levels remain within normal limits, the daily dosage may be decreased by one tablet every six months to a minimum effective dose. The maintenance dosage should not be reduced to the point where serum uric acid levels tend to rise.

**Therapy of Uncomplicated Gonorrhoea**

For the treatment of uncomplicated gonorrhoea in men or women, a single 1000 mg dose of Probenecid (2 tablets) may be given with adequate doses of oral ampicillin, intramuscularly injected aqueous procaine penicillin G or cefoxitin. If oral ampicillin is used, probenecid should be administered simultaneously. If a parenteral antibiotic is administered, the dose of probenecid should be given preferably at least 30 minutes before the injection.

**General Beta-lactam Antibiotic Therapy**

The adult recommended dosage is 2000 mg (4 tablets) daily in divided doses, reduced in older patients suspected of having renal impairment. Due to its mechanism of action, Probenecid is not recommended for concurrent use with a β-lactam antibiotic in the presence of known renal impairment.

**Children**

For two years of age or older the recommended dosage is 25 mg/kg (or 0.7 g/m² body surface) of body weight initially, followed by 40 mg/kg (or 1.2 g/m² body surface) daily in divided doses every six hours. For children weighing more than 50 kilograms the adult dose is recommended. The phenolsulfonphthalein (PSP) excretion test may be used to determine the effectiveness of probenecid in retarding penicillin excretion and maintaining therapeutic levels. When the dose of probenecid is adequate, the renal clearance of PSP is reduced to about one-fifth of the normal rate.
This product is not able to deliver all approved dose regimes.

**Contraindications**
- Hypersensitivity to any component of this product
- Persons with known blood dyscrasias
- Persons with uric acid kidney stones
- Children under 2 years of age
- Therapy with Probenecid should not be started until an acute gouty attack has subsided.

**Warnings and Precautions**
Use with caution in patients with a history of peptic ulcer.
The appearance of hypersensitivity reactions requires cessation of probenecid therapy.
If probenecid is given with methotrexate, the dosage of methotrexate should be reduced and serum levels may need to be monitored.
Haematuria, renal colic, costovertebral pain, and formation of urate stones associated with the use of probenecid in gouty patients may be prevented by alkalinisation of the urine and a liberal fluid intake. Sufficient sodium bicarbonate (3g to 7.5g daily) or potassium citrate (7.5g daily) is recommended to maintain alkaline urine. With such quantities of alkali, the acid-base balance of the patient should be watched.
Alkalisation of the urine is recommended until the serum acid level returns to normal (upper normal limit in males is about 6mg/100ml and in females, about 5mg/100ml) and tophaceous deposits disappear, i.e., during the period when urinary excretion of urates is at a high level. After the miscible pool of uric acid decreases to normal (about 1g) and deposited urates are re-sorbed and eliminated, alkalinisation of the urine probably is unnecessary, since the urinary urate concentration is lower and less likely to cause crystallisation.
Exacerbation of gout during therapy with probenecid may occur; in such cases, a therapeutic dosage of indomethacin, colchicine or other appropriate therapy should be added.

**Use during Pregnancy and Lactation**
Category B2
Probenecid crosses the placental barrier and appears in cord blood. The use of any medicine in women of childbearing potential requires that the anticipated benefit be weighed against possible hazards.
Reproduction studies in the rabbit and the rat at doses up to 10 times the recommended human dose have shown no evidence of teratogenic effects to the foetus due to probenecid.
Because animal reproduction studies are not always predictive of human response, probenecid should be used during pregnancy only if clearly needed.
It is not known whether the medicine is excreted in human milk. Because many medicines are excreted in human milk, caution should be exercised when probenecid is administered to a nursing mother.

**Adverse Effects**
Central Nervous System
Headache, dizziness
Gastrointestinal
nausea, anorexia, vomiting
Genitourinary
urinary frequency, in gouty patients exacerbation of gout, and uric acid stones with or without haematuria, renal colic, or costovertebral pain, have been observed, nephrotic syndrome occurs rarely
Hypersensitivity reactions
anaphylaxis, dermatitis, pruritus, urticaria, fever and Stevens-Johnson syndrome,
Haematological
anaemia, haemolytic anaemia which in some instances could be related to genetic deficiency
of glucose-6-phosphate dehydrogenase in red blood cells, leucopoenia and aplastic anaemia occur rarely.

Other exacerbation of gout, sore gums, flushing, alopecia, with toxic epidermal necrolysis reported rarely after combination therapy of colchicine and probenecid.

**Interactions**

In patients on probenecid the use of acetylsalicylic acid in either small or large doses is contraindicated because it antagonises the uricosuric action of probenecid. In patients on probenecid who require a mild analgesic agent the use of paracetamol rather than small doses of salicylates would be preferred.

Caution should be used if probenecid is administered simultaneously with methotrexate. Probenecid has been reported to decrease the tubular secretion of methotrexate and to potentiate toxicity.

Probenecid increases the mean plasma elimination half-life of a number of other medicines which can lead to increased peak plasma concentrations. These medicines include acetaminophen, naproxen, indomethacin, ketoprofen, meclofenamate, lorazepam, rifampin, acyclovir, ganciclovir and zidovudine. The clinical significance of this effect on plasma elimination half-life is not known; however, adjustment in the usual dosage of these medicines may be required.

Since probenecid decreases the renal excretion of conjugated sulfonamides, plasma concentrations of the latter should be determined from time to time when a sulfa medicine and probenecid are co-administered for prolonged periods. Probenecid may prolong or enhance the action of oral sulfonylureas and thereby increase the risk of hypoglycaemia.

The uricosuric action of probenecid is antagonised by pyrazinamide.

In animals, the renal tubular re-absorption of erythromycin is inhibited by probenecid and the renal excretion of sodium acetazolamide is decreased.

Because of its mechanism of action, probenecid is not recommended in conjunction with a β-lactam antibiotic in the presence of known renal impairment.

In addition to its effect on the excretion of uric acid, the β-lactam antibiotics (other than cephaloridine) probenecid decreases the urinary excretion of p-aminosalicylic acid (PAS), p-aminomethylphenic acid (PAH), phenolsulfonphthalein (PSP), pantothenic acid, 17-ketosteroids, sodium iodomethamate and related iodinated organic acids, probenecid decreases both hepatic and renal excretion of sulfobromophthalein (BSP). The renal tubular re-absorption of phosphorus is inhibited in hypoparathyroid but not in euparathyroid individuals.

A reducing substance may appear in the urine of patients receiving probenecid which may produce a false-positive Benedict's test leading to the possibility of a false diagnosis of glycosuria. However, this disappears with discontinuation of therapy.

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.

**Overdosage**

In the event of overdosage, symptomatic and supportive measures should be employed along with gastric lavage. If signs of central nervous excitation are present, a short-acting barbituate may be given parentally.

**Pharmaceutical Precautions**

Store below 25 °C.

**Medicines Classification**

Prescription Medicine
Package Quantities
Bottles of 100 tablets

Further Information
Tablets also contain maize starch.

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