NEW ZEALAND DATA SHEET

1 NAME OF THE MEDICINE

PROBENECID-AFT, Probenecid 500 mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg Probenecid.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Probenecid-AFT tablets are yellow capsule-shaped, film coated tablets, bisected on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Gout

For the treatment of hyperuricaemia in all stages of gout and gouty arthritis except a presenting acute attack.

Prophylactic treatment for relatives of gouty patients to forestall gouty attacks and urate deposition in tissues.

For control of hyperuricaemia induced or aggravated by diuretics.

β-Lactam Antibiotic Therapy

As an adjuvant to treatment with penicillin G or V, flucloxacillin, or cephalexin, for elevation and prolongation of plasma levels by whatever route the antibiotic is given.

4.2 DOSE AND METHOD OF ADMINISTRATION

Gout

Probenecid therapy should not be initiated until an acute gouty attack has subsided. However, if an acute attack is precipitated during therapy, probenecid may be continued without changing the dosage, and therapeutic doses of colchicine 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.

As uric acid tends to crystallise 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.

Alkalisation of the urine is recommended until the serum acid level returns to normal limits and tophaceous deposits disappear, i.e., during the period when urinary excretion of urates is at a high level. Alkalisation of the urine probably is unnecessary after the miscible pool of uric acid decreases to normal (about 1 g) and deposited urates are resorbed and eliminated, since the urinary urate concentration is lower and less likely to cause crystallisation.

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.

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.

Paediatric population

For two years of age or older the recommended dosage is 25 mg/kg (or 0.7 g/m^2 body surface) of body weight initially, followed by 40 mg/kg (or 1.2 g/m^2 body surface) daily in divided doses every six hours. For children weighing more than 50 kilograms the adult dose is recommended.

Method of administration

Tablets for oral administration.

4.3 CONTRAINDICATIONS

Probenecid is contraindicated in the following situations:

- Hypersensitivity to probenecid or to any of the excipients listed in section 6.1
- Patients with blood dyscrasias
- Patients with uric acid kidney stones
- Children under 2 years of age
- Starting treatment with probenecid during an acute gouty attack

- Coadministration with salicylates (see section 4.5 Interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Peptic ulcers

Use with caution in patients with a history of peptic ulcer.

Hypersensitivity

The appearance of hypersensitivity reactions requires cessation of probenecid therapy.

Use with methotrexate

If probenecid is given with methotrexate, the dosage of methotrexate should be reduced and serum levels may need to be monitored (see section 4.5).

Haematuria, renal colic, costovertebral pain

Haematuria, renal colic, costovertebral pain, and formation of urate stones associated with the use of probenecid in gouty patients may be prevented by alkalisation of the urine and a liberal fluid intake.

Sufficient sodium bicarbonate (3 g to 7.5 g daily) or potassium citrate (7.5 g daily) is recommended to maintain alkaline urine. With such quantities of alkali, the acid-base balance of the patient should be watched.

Exacerbation of gout

Exacerbation of gout during therapy with probenecid may occur; in such cases, a therapeutic dosage of colchicine or other appropriate therapy should be added.

Use in renal impairment

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

Probenecid may not be effective in chronic renal insufficiency, particularly when the glomerular filtration rate is 30 mL/min or less.

Effects on laboratory tests

Patients receiving probenecid may produce a false-positive Benedict's test leading to the possibility of a false diagnosis of glycosuria due to the presence of a reducing substance in the urine. This effect disappears when therapy is discontinued. Suspected glycosuria should be confirmed using a specific test for glucose, using enzymatic glucose oxidase reactions instead of copper reduction methods.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

General

Probenecid is a competitive inhibitor of organic anion transporters (OATs) in the kidney resulting in increased concentration of any concomitant medicines that are OAT

substrates. Probenecid also inhibits glucuronidation which increases concentrations of medicines metabolised through this pathway.

These medicines include paracetamol, naproxen, ketoprofen, lorazepam, rifampin, aciclovir, 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.

Aspirin and salicylates

The use of aspirin in either small or large doses is contraindicated because aspirin antagonises the uricosuric action of probenecid (see section 4.3 Contraindications). In patients on probenecid who require a mild analgesic agent the use of paracetamol rather than small doses of salicylates is preferred.

Methotrexate

Caution should be used if probenecid is administered simultaneously with methotrexate. Probenecid decreases the tubular secretion of methotrexate and may potentiate its toxicity.

Sulfonamides

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.

Sulfonylureas

Probenecid may prolong or enhance the action of oral sulfonylureas and thereby increase the risk of hypoglycaemia.

Pyrazinamide

The uricosuric action of probenecid is antagonised by pyrazinamide.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There were no adverse effects on reproductive parameters in groups of male and female SD rats, given probenecid in the diet at dose levels of 10, 50, and 100 mg/kg/day from 10 weeks prior to breeding and through the breeding of two successive litters.

Pregnancy

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.

Breastfeeding

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Although this medicine is unlikely to affect your ability to drive or operate machinery, a few people may be impaired and care should be taken.

4.8 UNDESIRABLE EFFECTS

Blood and lymphatic system disorders

Anaemia, haemolytic anaemia which in some instances could be related to genetic deficiency of glucose-6-phosphate dehydrogenase in red blood cells, leucopoenia, aplastic anaemia.

Immune system disorders

Anaphylaxis

Metabolism and nutrition disorders

Anorexia

Nervous system disorders

Headache, dizziness

Gastrointestinal disorders

Nausea, vomiting, sore gums

Hepatobiliary disorders

Hepatic necrosis

Skin and subcutaneous tissue disorders

Dermatitis, pruritus, urticaria, alopecia, Stevens-Johnson syndrome, toxic epidermal necrolysis reported rarely after combination therapy of colchicine and probenecid.

Musculoskeletal and connective tissue disorders

Exacerbation of gout

Renal and urinary disorders

Urinary frequency, uric acid stones with or without haematuria, renal colic, costovertebral pain, nephrotic syndrome

General disorders and administration site conditions

Fever, flushing

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

In massive overdosage, probenecid causes stimulation of the central nervous system which may lead to convulsions and death from respiratory failure. Symptomatic and supportive measures should be employed in the event of overdosage. Use activated charcoal, ideally within one hour of ingestion. Should signs of central nervous system excitation be present, a short-acting barbiturate may be given parenterally.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antigout preparations ATC code: M04AB01

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.

5.2 PHARMACOKINETIC PROPERTIES

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.

5.3 PRECLINICAL SAFETY DATA

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Maize starch
Microcrystalline cellulose(102)
Sodium Starch glycollate
Colloidal anhydrous silica
Magnesium stearate
Povidone K-30
Stearic acid (micronised)
Opadry yellow YS-1-2063
Opadry clearYS-1-7006

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

4 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER AND SPECIAL EQUIPMENT FOR USE, ADMINISTRATION OR IMPLANTATION

Probenecid Tablet 500 mg is packed in Milky White 100 cc HDPE Bottles & Milky White 38 mm HDPE caps with induction wad, which is labelled with Printed Sticker Labels.

Silica Gel Bags is used in packing as a preventive measure to absorb excess of moisture.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Not applicable.

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

04/02/2010

10 DATE OF REVISION OF THE TEXT

21 June 2024

SUMMARY TABLE OF CHANGES

Date	Sections(s) changed	Changes(s)
September 2021	6.3	Shelf life changed to 4 years.
June 2024	4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9	Sections re-worded as advised by Medsafe.