PRO-CID™

(PROBENECID TABLETS 500 MG)

1 NAME OF THE MEDICINE

Probenecid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PRO-CID tablet contains 500 mg probenecid.

Probenecid is a white or nearly white, fine, crystalline powder. It is slightly bitter with a pleasant aftertaste.

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

3 PHARMACEUTICAL FORM

PRO-CID 500 mg tablets are a yellow capsule-shaped film coated tablet, bisected on one side, with no embossing.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PRO-CID is indicated for:

Gout

Probenecid is a uricosuric agent for the treatment of hyperuricaemia in all stages of gout and gouty arthritis except an 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 (eg thiazides and similar diuretics).

β-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 benzylpenicillin, phenoxymethylpencillin, the synthetic penicillins, ampicillin, methicillin, oxacillin, cloxacillin, nafcillin, carbenicillin, and for the cephamycin, Mefoxin™ (cefoxitin sodium, MSD), and the cephalosporins, cephalothin, cephalexin and cephaloglycin.

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

Concurrent treatment with cidofovir for CMV retinitis in HIV patients

Probenecid is recommended to be administered concomitantly with cidofovir, as the combination reduces the potential for nephrotoxicity associated with cidofovir.

4.2 DOSE AND METHOD OF ADMINISTRATION

Tablet 500 mg probenecid, oral use.

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.

Adults

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 1 g 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 2 g 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.

To maintain an alkaline urine, sufficient sodium bicarbonate (3 g to 7.5 g daily) or potassium citrate (7.5 g daily) is recommended. When such quantities of alkali are administered, monitor the acid-base balance of the patient. Alkalisation of the urine is recommended until the serum uric acid level returns to normal and tophaceous deposits disappear, i.e. during the period when urinary excretion of urates is at a high level. Male normal upper limit is about 0.36 mmol/L. Female normal upper limit is about 0.30 mmol/L. 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 long term at a dosage that will maintain a normal serum uric acid level. If 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 this condition treatment in men or women, a single 1 g dose of PRO-CID (2 tablets) should be given with adequate doses of oral ampicillin, intramuscularly injected aqueous procaine penicillin 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 2 g PRO-CID (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.

Therapy with cidofovir

2 g PRO-CID (4 x 500 mg tablets) should be administered three hours before each dose of cidofivir and 1 gram (2 x 500 mg) tablets two and eight hours after the completion of the one hour infusion period (4 grams altogether). Evidence for a nephroprotective effect of probenecid with cidofovir was shown in a 52 week study conducted in cynomolgus monkeys.

Children

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

Note

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.

4.3 CONTRAINDICATIONS

PRO-CID is contraindicated in:

- Hypersensitivity to any component of this product
- Blood dyscrasias
- Uric acid stones
- Children less than two years of age
- Coadministration with salicylates.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use with caution

In patients with a history of peptic ulcer.

If given concurrently with methotrexate, the dosage of methotrexate should be reduced and serum levels may need to be monitored (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

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 (see Section 4.2 Dose and Method of Administration). When alkali is administered, the acid-base balance should be watched.

Should exacerbation of gout occur during therapy with probenecid, a therapeutic dose of indomethacin, colchicine or other appropriate therapy should be added.

If hypersensitivity reactions appear cease therapy with probenecid preparations.

Use in renal impairment

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

Use in the elderly

No data available.

Paediatric use

See Section 4.2 Dose and Method of Administration

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.

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Aspirin use 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 preferable.

Pyrazinamide also antagonises the uricosuric action of probenecid.

If methotrexate is given concurrently, its dosage should be reduced and serum levels may need to be monitored. Probenecid decreases the tubular secretion of methotrexate and may potentiate its toxicity.

Probenecid increases the mean plasma elimination half-life of paracetamol, naproxen, ciprofloxacin, indomethacin, ketoprofen, meclofenamate, rifampicin, valaciclovir/aciclovir, famiciclovir/penciclovir, ganciclovir, zidovudine, dapsone, ketorolac, lorazepam, midazolam, and nitrazepam (not temazepam). Increased plasma concentrations and adverse events may result requiring an adjustment in the usual dosage of these drugs.

Allopurinol and probenecid used together may both have increased plasma concentrations.

Since probenecid decreases the renal excretion of conjugated sulfonamides, plasma concentrations of the latter should be determined from time to time when coadministration for prolonged periods occurs.

Probenecid may prolong or enhance the action of oral sulfonylureas and thereby increase the risk of hypoglycaemia. Probenecid may also potentiate the effects of *thiazide diuretics.*

Less thiopental for induction of anaesthesia may be required. Ketamine and thiopental anaesthesia may be prolonged.

Probenecid has also been reported to inhibit the renal transport of many other compounds including *p*-aminohippuric acid (PAH), p-aminosalicylic acid (PAS), panthothenic acid, indomethacin, famotidine, sodium

iodomethamate and related iodinated organic acids, sodium acetrizoate, erythromycin, 17-ketosteroids, pantothenic acid, phenolsulfonphthalein (PSP) and cephalosporins (excluding ceftazidime and ceftriaxone). It decreases both hepatic and renal secretion of sulfobromophthalein (BSP).

Probenecid does not influence plasma salicylate concentrations, nor does it affect the excretion of streptomycin, chloramphenicol, chlortetracycline, oxytetracycline, or neomycin. The effects on excretion of cephaloridine are not clinically significant.

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.

Use in pregnancy

Probenecid is Pregnancy Category B2 - *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.*

Probenecid crosses the placental barrier and appears in cord blood. The use of any drug in women of childbearing potential requires that the anticipated benefit be weighed against possible hazards.

Use in lactation

It is not known whether this drug is excreted in human or animal milk. Because many drugs 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

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

CNS: Headache, dizziness.

Gastrointestinal: Nausea, anorexia, vomiting, sore gums. Hepatic necrosis occurs rarely.

Genitourinary: In gouty patients, uric acid stones with or without haematuria, renal colic or costovertebral pain has been observed. Nephrotic syndrome occurs rarely. Urinary frequency has been reported.

Hypersensitivity: Anaphylaxis, fever, pruritus, urticaria, Stevens-Johnson syndrome.

Haematologic: Anaemia, haemolytic anaemia which could be related to genetic deficiency of glucose-6-phosphate dehydrogenase in red blood cells. Aplastic anaemia, leucopenia and thrombocytopenia occur rarely.

Integumentary: Alopecia, dermatitis, flushing. After combination therapy of colchicine and probenecid toxic epidermal necrolysis has been reported rarely.

Musculoskeletal: Exacerbation of gout.

Retinopathy has been reported once in conjunction with chloroquine.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

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 information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 euparathyroid individuals.

Probenecid increases plasma concentrations of methotrexate in both animals and humans. In animal studies, increased methotrexate toxicity has been reported.

Clinical trials

No data available.

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 nonlinear disposition.

Excretion

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

Genotoxicity

No evidence of mutagenicity was observed in a microbial mutagenicity test using mutant strains of *Salmonella typhimurium* with or without rat or hamster liver metabolic activation. No genetic damage was noted in a chromosome aberration study in CHO cells. Variable results were obtained in a sister chromatid exchange (SCE) test in CHO cells. One trial caused a dose-related increase in SCE's, a second trial was negative, and a third trial had significant increases at the lowest and highest doses tested (but not in the intermediate doses).

Carcinogenicity

In a 23-month carcinogenic study in mice, a significant increase in the incidence of hepatocellular carcinomas and adenomas was observed at a dose of 400 mg/kg/day in female mice. These changes were not observed in male mice or rats of either sex that received the same dose, or in mice of either sex at a dose of 100 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The excipients are cellulose microcrystalline, starch (maize), sodium starch glycollate, stearic acid, povidone, silica colloidal anhydrous, magnesium stearate and opadry yellow and opadry clear.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG)[1]. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C in a dry place.

6.5 NATURE AND CONTENTS OF CONTAINER

PRO-CID is supplied in a bottle of 100 tablets.

Phebra product code - TAB009

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

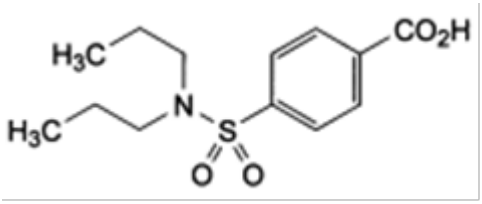
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Name: 4-(dipropylsulphamoyl) benzoic acid, calculated with reference to the dried substance.

The molecular weight of the compound is 285.4. The molecular formula is $C_{13}H_{19}NO_4S$.

Chemical structure



CAS number

57-66-9

Probenecid is soluble in chloroform, dilute alkali, alcohol, and acetone, and practically insoluble in water and dilute acids. It is soluble in dilute solutions of sodium hydroxide which can be buffered to pH 7.4 with monopotassium phosphate or other similar buffer.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

[1] AUST R 74598

8 SPONSOR

Phebra[2] Pty Ltd

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Telephone: 1800 720 020

9 DATE OF FIRST APPROVAL

5 Jun 2000

10 DATE OF REVISION

5 Sep 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
NA	PI reformatted to align with new form
6.4	Change of storage condition from 25ºC to 30ºC

[2] PRO-CID, Phebra and the Phi symbol are trademarks of Phebra Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.