Antigout Drugs

This chapter deals with the treatment of gout and hyperuricaemia and the drugs used mainly for these disorders.

Gout and hyperuricaemia

Uric acid is the final product of the metabolism of endogenous and exogenous purine in man. An excess of uric acid, measured in the plasma as sodium urate, constitutes **hyperuricaemia**. This excess may be caused by an overproduction or underexcretion of urate. It is influenced by genetic and environmental factors and may be classified as primary (mainly idiopathic) or secondary. An increase in urate production may be caused by excessive dietary purine intake, certain cancers or their treatment, or, more rarely, enzyme defects of purine metabolism. Reduced urate excretion may be caused by renal disease, hypertension, or the intake of certain drugs such as thiazide diuretics. Other factors contributing to hyperuricaemia include hyperlipidaemia, obesity, alcohol consumption, and lead exposure.

A patient is usually considered to be hyperuricaemic when plasma-urate concentrations exceed 0.42 mmol/litre (7 mg per 100 mL) in men and postmenopausal women or 0.36 mmol/litre (6 mg per 100 mL) in premenopausal women. At these high concentrations there is a risk of crystals of monosodium urate monohydrate being formed and deposited in synovial fluid and various tissues. However, some subjects may have supersaturated plasma-urate concentrations without any crystal deposits, while others may suffer from deposits in the absence of apparent hyperuricaemia.

The presence of urate crystals in the synovial fluid leads to an inflammatory response in the affected joint, commonly at the base of the big toe (podagra). The ensuing exquisite pain, tenderness, erythema, and swelling constitute the clinical manifestations of **acute inflammatory gouty arthritis**. Repeated acute attacks may be associated with a visible or palpable build up of crystal deposits (**tophi**) at various sites including in and around the affected joint. Tophi release urate crystals into the synovial fluid after various stimuli and so cause further acute attacks, leading to **chronic tophaceous gout**. Intra-articular and peri-articular tophi may cause gradual joint erosion, which, without treatment, results in disabling **chronic gouty arthritis**. Rarely, the kidney can be affected by urate deposits producing a gouty nephropathy or by uric acid calculi or stones (uric acid nephrolithiasis or urolithiasis).

Treatment aims to alleviate the acute attack, prevent future attacks, and lower plasma-urate concentration.

Plasma-urate concentrations may be reduced by control of obesity and modification of diet and alcohol intake. Drug treatment can relieve the pain of acute attacks but more prolonged therapy for hyperuricaemia is generally only considered if there are recurrent attacks of gout or there is renal involvement (see under Chronic Gout, below).

Acute gout. An attack of acute inflammatory gouty arthritis is best treated as soon as possible with an NSAID. Aspirin or other salicylates are not suitable since they may increase plasma-urate concentrations. Treatment is started with high doses of an NSAID, the doses being reduced as the patient responds. Usually treatment can be withdrawn within 1 to 2 weeks. Colchicine is an effective alternative; it may be used alone, or with an NSAID. Patients who do not respond to NSAIDs or colchicine, or for whom these drugs are contra-indicated, may be treated with a systemic corticosteroid. Intra-articular corticosteroids are effective in acute monoarticular gout, or when used adjunctively in patients with polyarticular gout; infection of joints should be excluded prior to injection. Intravenous, intramuscular, or subcutaneous corticotropin has been reported to alleviate pain and inflammation in acute gout. It may be used alone or adjunctively, and may be a useful alternative in patients with renal and gastrointestinal contra-indications to other therapies. Other therapies for acute gout include adjunctive analgesics and topical ice. Drugs used for chronic gout (allopurinol or the uricosurics) should not be started during an acute attack since they can exacerbate and prolong it (see below).

Chronic gout. If the patient suffers frequent acute attacks or develops tophaceous gout, or has renal complications as a result of urate overproduction, then long-term treatment of hyperuricaemia may be needed. Such **urate-lowering therapy** should not be started during an acute attack, or for 2 to 3 weeks thereafter, as fluctuations in urate concentration may prolong the existing attack or initiate a new one. Treatment involves inhibiting the production of uric acid or enhancing its urinary excretion, in order to maintain a serum urate concentration at or below 0.3 or 0.36 mmol/litre. Hyperuricaemia due to overproduction of urate is treated with allopurinol which inhibits the enzyme xanthine oxidase, involved in purine metabolism. Hyperuricaemia associated with underexcretion of uric acid can be treated with either allopurinol or a uricosuric such as benzbromarone, probenecid or sulfinpyrazone. Allopurinol is most commonly given as first-line therapy, but may be combined with or replaced by uricosurics if treatment fails. Allopurinol should also be used for patients with renal urate deposits or with uric acid renal calculi as it reduces urolithiasis. Febuxostat is an alternative xanthine oxidase inhibitor under investigation.

With either treatment there is mobilisation of urate crystals from established tophi, as the plasma-urate concentration falls, which can trigger further acute attacks of gout. Patients are thus also given **prophylaxis** with an NSAID or colchicine from the start of urate-lowering treatment until at least a month after the plasma-urate has been reduced to an acceptable concentration; up to 6 months of prophylactic cover has been recommended.

Once the hyperuricaemia is corrected, the patient continues to receive therapy with allopurinol or uricosurics indefinitely. If an acute attack occurs during such maintenance therapy, this therapy should be continued to avoid fluctuations in urate concentration, and the acute attack treated in its own right.

Surgery may have to be considered for patients severely affected by chronic tophaceous gout.

References[1-18] to gout and its management are given below.

1. Agudelo CA, Wise CM. Gout: diagnosis, pathogenesis, and clinical manifestations. *Curr Opin Rheumatol* 2001; **13:** 234–9.
2. Schlesinger N, Schumacher HR. Gout: can management be improved? *Curr Opin Rheumatol* 2001; **13:** 240–4.
3. Terkeltaub RA. Gout. *N Engl J Med* 2003; **349:** 1647–55.
4. Rott KT, Agudelo CA. Gout. *JAMA* 2003; **289:** 2857–60.
5. Snaith ML, Adebajo AO. Gout and hyperuricaemia. In: Snaith ML, ed. *ABC of rheumatology.* 3rd ed. London: BMJ Publishing Group, 2004: 39–44.
6. Anonymous. Gout in primary care. *Drug Ther Bull* 2004; **42:** 37–40.
7. Schlesinger N. Management of acute and chronic gouty arthritis: present state-of-the-art. *Drugs* 2004; **64:** 2399–2416.
8. Wortmann RL. Recent advances in the management of gout and hyperuricemia. *Curr Opin Rheumatol* 2005; **17:** 319–24.
9. Underwood M. Gout. *Clin Evid* 2005; **13:** 1435–44.
10. Suresh E. Diagnosis and management of gout: a rational approach. *Postgrad Med J* 2005; **81:** 572–9.
11. Stamp L, *et al.* Gout in solid organ transplantation: a challenging clinical problem. *Drugs* 2005; **65:** 2593–2611.
12. Choi HK, *et al.* Pathogenesis of gout. *Ann Intern Med* 2005; **143:** 499–516.
13. Lee SJ, *et al.* Recent developments in diet and gout. *Curr Opin Rheumatol* 2006; **18:** 193–8.
14. Teng GG, *et al.* Pathophysiology, clinical presentation and treatment of gout. *Drugs* 2006; **66:** 1547–63.
15. Underwood M. Diagnosis and management of gout. *BMJ* 2006; **332:** 1315–19.
16. Zhang W, *et al.* EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006; **65:** 1312–24.
17. Jordan KM, *et al.* British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology (Oxford)* 2007; **46:** 1372–4. Also available at: http://rheumatology.oxfordjournals.org/cgi/reprint/46/8/1372 (accessed 22/04/08)
18. Schlesinger N. Overview of the management of acute gout and the role of adrenocorticotropic hormone. *Drugs* 2008; **68:** 407–15.

Allopurinol *(BAN, USAN, rINN)*

Allopürinol; Allopurinoli; Allopurinolum; Allopurynol; Alopurinol; Alopurinolis; BW-56-158; HPP; NSC-1390.

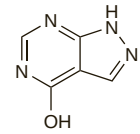
Аллопуринол

$C_5H_4N_4O$ = 136.1.

CAS — 315-30-0 (allopurinol); 17795-21-0 (allopurinol sodium).

ATC — M04AA01.

ATC Vet — QM04AA01.



Description. Allopurinol is a tautomeric mixture of 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol and 1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Allopurinol). A white or almost white powder. Very slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides.

USP 31 (Allopurinol). A fluffy white to off-white powder having only a slight odour. Very slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether; soluble in solutions of potassium and sodium hydroxides.

Incompatibility. Allopurinol sodium as a 3 mg/mL solution in 0.9% sodium chloride was visually incompatible with amikacin sulfate, amphotericin B, carmustine, cefotaxime sodium, chlormethine hydrochloride, chlorpromazine hydrochloride, cimetidine hydrochloride, clindamycin phosphate, cytarabine, dacarbazine, daunorubicin hydrochloride, diphenhydramine hydrochloride, doxorubicin hydrochloride, doxycycline hyclate, droperidol, floxuridine, gentamicin sulfate, haloperidol lactate, hydroxyzine hydrochloride, idarubicin hydrochloride, imipenem with cilastatin sodium, methylprednisolone sodium succinate, metoclopramide hydrochloride, minocycline hydrochloride, nalbuphine hydrochloride, netilmicin sulfate, ondansetron hydrochloride, pethidine hydrochloride, prochlorperazine edisilate, promethazine hydrochloride, sodium bicarbonate, streptozocin, tobramycin sulfate, and vinorelbine tartrate.[1]

1. Trissel LA, Martinez JF. Compatibility of allopurinol sodium with selected drugs during simulated Y-site administration. *Am J Hosp Pharm* 1994; **51:** 1792–9.

Adverse Effects

The most common adverse effect of allopurinol is skin rash. Rashes are generally maculopapular or pruritic, sometimes purpuric, but more serious hypersensitivity reactions may occur and include exfoliative rashes, the Stevens-Johnson syndrome, and toxic epidermal necrolysis. It is therefore recommended that allopurinol be withdrawn immediately if a rash occurs (see Precautions, below). Further symptoms of hypersensitivity include fever and chills, lymphadenopathy, leucopenia or leucocytosis, eosinophilia, arthralgia, and vasculitis leading to renal and hepatic damage and, very rarely, seizures. These hypersensitivity reactions may be severe, even fatal, and patients with hepatic or renal impairment are at special risk.

Hepatotoxicity and signs of altered liver function may also be found in patients who are not hypersensitive. Haematological effects include thrombocytopenia, aplastic anaemia, agranulocytosis, and haemolytic anaemia.

Many other adverse effects have been noted rarely and include paraesthesia, peripheral neuropathy, alopecia, gynaecomastia, hypertension, taste disturbances, nausea, vomiting, abdominal pain, diarrhoea, headache, malaise, drowsiness, vertigo, and visual disturbances.

Patients with gout may have an increase in acute attacks on beginning treatment with allopurinol, although attacks usually subside after several months.

Incidence of adverse effects. A Boston Collaborative Drug Surveillance Program involving 29 524 hospitalised patients found that, with the exception of skin reactions, 33 of 1835 patients treated with allopurinol (1.8%) had adverse effects. These effects were dose-related and the most frequent were haematological (11 patients, 0.6%), diarrhoea (5 patients, 0.3%), and drug fever (5 patients, 0.3%). Hepatotoxicity was reported in 3 patients (0.2%). Two patients developed possible hypersensitivity reactions to allopurinol.[1]

A further analysis involving 1748 outpatients indicated no instances of acute blood disorders, skin diseases, or hypersensitivity that warranted hospital treatment. Liver disease, although found, was not considered to be associated with allopurinol.

There were only 2 patients in whom renal disease could possibly have been caused by allopurinol.[2]

1. McInnes GT, *et al*. Acute adverse reactions attributed to allopurinol in hospitalised patients. *Ann Rheum Dis* 1981; **40:** 245–9.
2. Jick H, Perera DR. Reactions to allopurinol. *JAMA* 1984; **252:** 1411.

Effects on the blood. In addition to the haematological abnormalities of leucopenia, thrombocytopenia, haemolytic anaemia, and clotting abnormalities noted in the Boston Collaborative Drug Surveillance Program,[1] aplastic anaemia has also been reported, sometimes in patients with renal impairment.[2] Pure red cell aplasia has also been reported.[3,4]

1. McInnes GT, *et al*. Acute adverse reactions attributed to allopurinol in hospitalised patients. *Ann Rheum Dis* 1981; **40:** 245–9.
2. Anonymous. Allopurinol and aplastic anaemia. *WHO Drug Inf* 1989; **3:** 26.
3. Lin Y-W *et al.* Acute pure red cell aplasia associated with allopurinol therapy. *Am J Hematol* 1999; **61:** 209–11.
4. Chao S-C, *et al*. Hypersensitivity syndrome and pure red cell aplasia following allopurinol therapy in a patient with chronic kidney disease. *Ann Pharmacother* 2005; **39:** 1552–6.

Effects on the eyes. Some case reports have suggested an association between allopurinol use and the development of cataracts,[1] but a detailed ophthalmological survey involving 51 patients who had taken allopurinol failed to confirm this.[2] However, a large retrospective case-control study in elderly patients concluded that long-term, or high-dose, allopurinol therapy did increase the risk of cataract extraction.[3]

1. Fraunfelder FT, *et al*. Cataracts associated with allopurinol therapy. *Am J Ophthalmol* 1982; **94:** 137–40.
2. Clair WK, *et al*. Allopurinol use and the risk of cataract formation. *Br J Ophthalmol* 1989; **73:** 173–6.
3. Garbe E, *et al.* Exposure to allopurinol and the risk of cataract extraction in elderly patients. *Arch Ophthalmol* 1998; **116:** 1652–6.

Effects on the skin. Skin reactions are the most common adverse effects of allopurinol.

One report calculated that of 215 adverse effects noted over a 16-year period 188 (87.4%) were related to the skin or mucous membranes.[1] An analysis by the Boston Collaborative Drug Surveillance Program of data on 15 438 patients hospitalised between 1975 and 1982 detected 6 allergic skin reactions attributed to allopurinol among 784 recipients of the drug.[2] Desensitisation protocols[3] and alternative drugs[4] have been used after cutaneous reactions to allopurinol.

Serious skin reactions to allopurinol may occur as part of a generalised hypersensitivity reaction. A review of the literature between 1970 and the end of 1990 revealed 101 cases of allopurinol hypersensitivity syndrome, 94 of which involved the skin.[5] Skin reactions included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, or a diffuse maculopapular or exfoliative dermatitis; 27 of the 101 patients died. The relative risk of toxic epidermal necrolysis or Stevens-Johnson syndrome occurring with allopurinol was high (calculated to be 5.5) in a case-control study including 13 patients with these cutaneous reactions who had received allopurinol.[6] This risk was not constant over time, being higher during the first 2 months of treatment. During these 2 months the estimated excess risk was 1.5 cases per million users per week. Another case-control study,[7] involving 379 patients with Stevens-Johnson syndrome or toxic epidermal necrolysis, found that allopurinol was the drug most frequently associated with these reactions. The risk again appeared to be restricted to short-term use (less than 8 weeks) and was greater in patients taking 200 mg or more daily.

1. Vinciullo C. Allopurinol hypersensitivity. *Med J Aust* 1984; **141:** 449–50.
2. Bigby M, *et al.* Drug-induced cutaneous reactions. *JAMA* 1986; **256:** 3358–63.
3. Fam AG, *et al.* Efficacy and safety of desensitization to allopurinol following cutaneous reactions. *Arthritis Rheum* 2001; **44:** 231–8.
4. Fam AG. Difficult gout and new approaches for control of hyperuricemia in the allopurinol-allergic patient. *Curr Rheumatol Rep* 2001; **3:** 29–35.
5. Arellano F, Sacristán JA. Allopurinol hypersensitivity syndrome: a review. *Ann Pharmacother* 1993; **27:** 337–43.
6. Roujeau J-C, *et al.* Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333:** 1600–1607.
7. Halevy S, *et al.* EuroSCAR Study Group. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J Am Acad Dermatol* 2008; **58:** 25–32.

Precautions

Allopurinol should not be used for the treatment of an acute attack of gout; additionally, allopurinol therapy should not be begun for any purpose during an acute attack. However, allopurinol is continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately.

Treatment should be stopped immediately if any skin reactions or other signs of hypersensitivity develop. A cautious reintroduction at a low dose may be attempted when mild skin reactions have cleared (see Effects on the Skin, above); allopurinol should not be reintroduced in those patients who have experienced other forms of hypersensitivity reaction. Dosage should be reduced in renal or hepatic impairment. Care is advised in patients being treated for hypertension or cardiac insufficiency, who may also have renal impairment.

To reduce the risk of renal xanthine deposition an adequate fluid intake (2 to 3 litres daily) is required. In addition, a neutral or slightly alkaline urine may be desirable.

Breast feeding. Allopurinol and its metabolite, oxipurinol, are distributed into breast milk, and licensed product information recommends that allopurinol should be used with caution in breast-feeding women. Although oxipurinol was detected in the plasma of a breast-fed infant, no adverse effects were noted in the infant during 6 weeks of maternal treatment with allopurinol.[1] The American Academy of Pediatrics noted that there had been no documented problems with allopurinol and considered its use to be usually compatible with breast feeding.[2]

1. Kamilli I, Gresser U. Allopurinol and oxypurinol in human breast milk. *Clin Investig* 1993; **71:** 161–4.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)

Interactions

Drugs that can increase uric acid concentrations may decrease the efficacy of allopurinol. Aspirin and the salicylates possess this activity and should generally be avoided in hyperuricaemia and gout. An increase in hypersensitivity reactions, and possibly also other adverse effects, has been reported in patients taking allopurinol with ACE inhibitors or thiazide diuretics, particularly in patients with renal impairment.

The metabolism of azathioprine and mercaptopurine is inhibited by allopurinol and their doses should be markedly reduced when either of them is given with allopurinol to avoid potentially life-threatening toxicity. There have also been reports of allopurinol enhancing the activity of, and possibly increasing the toxicity of, a number of other drugs including some antibacterials, some anticoagulants, some other antineoplastics, ciclosporin, some sulfonylurea antidiabetics, theophylline, and vidarabine.

ACE inhibitors. An apparent interaction between allopurinol and *captopril* has been reported in patients with chronic renal failure. In one patient it was suggested that the development of fatal Stevens-Johnson syndrome after the introduction of allopurinol was due to potentiation by captopril.[1] In the second patient hypersensitivity, characterised by fever, arthralgia, and myalgia, occurred and was believed to be due to captopril, or one of its metabolites, potentiated by the addition of allopurinol.[2] Care is advised if allopurinol is used with captopril, especially in patients with chronic renal failure.

1. Pennell DJ, *et al*. Fatal Stevens-Johnson syndrome in a patient on captopril and allopurinol. *Lancet* 1984; **i:** 463.
2. Samanta A, Burden AC. Fever, myalgia, and arthralgia in a patient on captopril and allopurinol. *Lancet* 1984; **i:** 679.

Antacids. Allopurinol failed to reduce blood-uric-acid concentrations when given at the same time as *aluminium hydroxide* in 3 patients on chronic haemodialysis. However, if allopurinol was given 3 hours before aluminium hydroxide the expected decrease in uric acid concentration did occur.[1]

1. Weissman I, Krivoy N. Interaction of aluminium hydroxide and allopurinol in patients on chronic hemodialysis. *Ann Intern Med* 1987; **107:** 787.

Antibacterials. Although an increased incidence of skin rashes has been noted when allopurinol has been used with *ampicillin* or *amoxicillin*, data currently available are insufficient to confirm whether this is due to allopurinol or not. For further details, see Ampicillin, p.204.

Anticoagulants. For the effect of allopurinol on *dicoumarol*, *phenprocoumon*, or *warfarin*, see Warfarin, p.1429.

Antiepileptics. For a report of allopurinol possibly inhibiting the metabolism of *phenytoin*, see under Antigout Drugs, p.499.

Antigout drugs. Uricosuric drugs are likely to increase the renal elimination of oxipurinol (the major active metabolite of allopurinol). For example, *benzbromarone* lowered plasma concentrations of oxipurinol by about 40% when used with allopurinol, although plasma concentrations of allopurinol itself were not affected.[1] The interaction was not of concern, since the combination was more effective than allopurinol alone in lowering serum concentrations of uric acid. Licensed product information recommends reassessing the dosage of allopurinol on an individual basis when a uricosuric drug is added.

Probenecid has been reported to decrease the clearance of oral allopurinol riboside.[2] In a pharmacokinetic study in healthy subjects,[3] giving allopurinol and probenecid together significantly reduced oxipurinol concentrations; however, this combination had a greater hypouricaemic effect than either drug given alone.

1. Müller FO, *et al*. The effect of benzbromarone on allopurinol/oxypurinol kinetics in patients with gout. *Eur J Clin Pharmacol* 1993; **44:** 69–72.
2. Were JBO, Shapiro TA. Effects of probenecid on the pharmacokinetics of allopurinol riboside. *Antimicrob Agents Chemother* 1993; **37:** 1193–6.
3. Stocker SL, *et al.* Pharmacokinetic and pharmacodynamic interaction between allopurinol and probenecid in healthy subjects. *Clin Pharmacokinet* 2008; **47:** 111–18.

Antineoplastics. Allopurinol inhibits the metabolism of *mercaptopurine* and marked dosage reduction of this drug to one-quarter to one-third of the usual dose is required if it is used with allopurinol. There are also reports of interactions between allopurinol and other antineoplastics. Mild chronic allopurinol-induced hepatotoxicity has been reported in a male patient to have been exacerbated by *tamoxifen*.[1] Hypersensitivity vasculitis resulting in the death of a patient receiving allopurinol and *pentostatin* has been described. Although it could not be ascertained whether this effect was due to one of the drugs alone or to an interaction it was believed that this combination should not be used.[2]

For a report of an increased incidence of bone-marrow toxicity in patients given allopurinol with *cyclophosphamide*, see p.703.

1. Shah KA, *et al.* Allopurinol hepatotoxicity potentiated by tamoxifen. *N Y State J Med* 1982; **82;** 1745–6.
2. Steinmetz JC, *et al.* Hypersensitivity vasculitis associated with 2-deoxycoformycin and allopurinol therapy. *Am J Med* 1989; **86:** 499.

Antivirals. For the effect of allopurinol on *didanosine*, see p.871.

Immunosuppressants. Allopurinol inhibits the metabolism of mercaptopurine, the metabolite of *azathioprine*, and marked dosage reduction of azathioprine to one-quarter to one-third of the usual dose is required if it is used with allopurinol. Similar caution is also required with mercaptopurine itself (see Antineoplastics, above). The effects of allopurinol on *ciclosporin* concentrations (a marked increase) are reported on p.1826.

Xanthines. For the effect of allopurinol on the pharmacokinetics of *caffeine* and *theophylline*, see p.1117 and p.1144 respectively.

Pharmacokinetics

Up to 90% of an oral dose of allopurinol is rapidly absorbed from the gastrointestinal tract; its plasma half-life is about 1 to 2 hours. Allopurinol's major metabolite is oxipurinol (alloxanthine), which is also an inhibitor of xanthine oxidase with a plasma half-life of about 15 or more hours in patients with normal renal function, although this is greatly prolonged by renal impairment. Both allopurinol and oxipurinol are conjugated to form their respective ribonucleosides. Allopurinol and oxipurinol are not bound to plasma proteins.

Excretion is mainly through the kidney, but it is slow since oxipurinol undergoes tubular reabsorption. About 70% of a daily dose may be excreted in the urine as oxipurinol and up to 10% as allopurinol; prolonged use may alter these proportions, as allopurinol inhibits its own metabolism. The remainder of the dose is excreted in the faeces. Allopurinol and oxipurinol have also been detected in breast milk.

◊ References.

1. Murrell GAC, Rapeport WG. Clinical pharmacokinetics of allopurinol. *Clin Pharmacokinet* 1986; **11:** 343–53.
2. Turnheim K, *et al*. Pharmacokinetics and pharmacodynamics of allopurinol in elderly and young subjects. *Br J Clin Pharmacol* 1999; **48:** 501–9.
3. Day RO, *et al.* Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. *Clin Pharmacokinet* 2007; **46:** 623–44.

Uses and Administration

Allopurinol is used to treat hyperuricaemia (p.552) associated with chronic gout, acute uric acid nephropathy, recurrent uric acid stone formation, certain enzyme disorders, or cancer and its treatment (see Tumour Lysis Syndrome, p.639). It is not used for asymptomatic hyperuricaemia. Allopurinol is also used in the management of renal calculi caused by the deposition of calcium oxalate (in the presence of hyperuricosuria) and of 2,8-dihydroxyadenine (see Renal Calculi, below). It may have the potential to reduce oxidative stress by blocking the production of free radicals and is an ingredient of kidney preservation solutions. In addition allopurinol has antiprotozoal activity and has been used in leishmaniasis and American trypanosomiasis.

Allopurinol is used in **gout and hyperuricaemia** to inhibit the enzyme xanthine oxidase, thus preventing the oxidation of hypoxanthine to xanthine and xanthine to uric acid. The urinary purine load, normally almost entirely uric acid, is thereby divided between hypoxanthine, xanthine, and uric acid, each with its independent solubility. This results in the reduction of urate and uric acid concentrations in plasma and urine, ideally to such an extent that deposits of monosodium urate monohydrate or uric acid are dissolved or prevented from forming. At low concentrations allopurinol acts as a competitive inhibitor of xanthine oxidase and at higher concentrations as a non-competitive inhibitor. However, most of its activity is due to the metabolite oxipurinol which is a non-competitive inhibitor of xanthine oxidase.

Allopurinol is used in chronic gout to correct hyperuricaemia, reduce the likelihood of acute attacks, and prevent the sequelae of chronic gout. Initially, it may increase plasma-concentrations of urate and uric acid by dissolving deposits. This can trigger or exacerbate acute attacks, hence allopurinol should not be started until an acute attack has completely subsided, and treatment should be started with a low dose increased gradually; an NSAID (but not aspirin or salicylates) or colchicine should also be given for at least 1 month after hyperuricaemia is corrected, usually 3 months. It may take several months to deplete the uric acid level sufficiently to control acute attacks.

A suggested oral starting dose of allopurinol is 100 mg daily, gradually increased by 100 mg for example at weekly intervals until the concentration of urate in plasma is reduced to 0.36 mmol/litre (6 mg per 100 mL) or less. A daily dose range of 100 to 300 mg may be adequate for those with mild gout and up to 600 mg for those with moderately severe tophaceous gout. The maximum recommended daily dose is 800 mg in the USA and 900 mg in the UK. Up to 300 mg may be taken as a single daily dose; larger amounts should be taken in divided doses to reduce the risk of gastric irritation. Taking allopurinol after food will also minimise gastric irritation. Patients should maintain an adequate fluid intake to prevent renal xanthine deposition.

Doses of allopurinol should be reduced in patients with renal impairment (see below)

When used for the prevention of uric acid nephropathy associated with cancer therapy 600 to 800 mg may be given daily, generally for 2 or 3 days before starting the cancer treatment. A high fluid intake is essential. In hyperuricaemia secondary to cancer or cancer chemotherapy, maintenance doses of allopurinol are similar to those used in gout and are given according to the response.

The main use of allopurinol in children is for hyperuricaemia associated with cancer or cancer chemotherapy or with enzyme disorders. The dosage used may vary: in the UK a dose of 10 to 20 mg/kg daily up to a maximum of 400 mg daily is recommended for children under 15 years of age, while in the USA the dose is 150 mg daily for children under 6 years of age and 300 mg daily for those aged 6 to 10 years, adjusted if necessary after 48 hours.

Allopurinol sodium has been given by intravenous infusion in sodium chloride 0.9% or glucose 5% to patients (usually cancer patients) unable to take allopurinol orally. The recommended dose in adults is the equivalent of allopurinol 200 to 400 mg/m^2 daily up to a maximum of 600 mg daily. Allopurinol sodium 116.2 mg is equivalent to 100 mg of allopurinol.

Administration in renal impairment. Excretion of allopurinol and its active metabolite oxipurinol is primarily via the kidneys and therefore the dosage should be reduced in renal impairment according to creatinine clearance (CC).

In the USA the following doses are suggested for oral and intravenous use:

- CC 10 to 20 mL/minute: 200 mg daily
- CC less than 10 mL/minute: no more than 100 mg daily
- CC less than 3 mL/minute: consider also a longer dosage interval

In the UK a maximum initial oral daily dosage of 100 mg is recommended for those with renal impairment, increased only if the response is inadequate. Doses less than 100 mg daily or 100 mg at intervals longer than 1 day are recommended for those with severe renal insufficiency. Because of the imprecision of low creatinine clearance values, it is suggested that, if facilities are available for monitoring, the allopurinol dose should be adjusted to maintain plasma-oxipurinol concentrations below 100 micromoles/litre (15.2 micrograms/mL). A suggested alternative dose for patients requiring dialysis two or three times weekly is 300 to 400 mg allopurinol immediately after dialysis only.

The difficulties of maintaining an appropriate dose in such patients were illustrated by a study[1] in New Zealand involving 227 allopurinol-treated patients. The guidelines used suggested maintenance doses based on CC as follows:

- less than 10 mL/minute: 100 mg every 3 days
- 10 mL/minute: 100 mg every 2 days
- 20 mL/minute: 100 mg daily
- 40 mL/minute: 150 mg daily
- 60 mL/minute: 200 mg daily

The recommended dose or less was used in the majority of cases (183 of 227). However, of 214 patients for whom serum-uric acid concentrations were available, only 48 achieved values of 0.36 mmol/litre or less. The proportion of patients achieving acceptable serum-uric acid concentrations was higher (38%) in patients given higher than recommended doses than in those on doses recommended by the guidelines (19%). Although guidelines might be useful for initial dosing, longer term use could lead to inadequate control of hyperuricaemia.

1. Dalbeth N, *et al.* Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. *J Rheumatol* 2006; **33:** 1646–50.

Diagnosis and testing. Deficiency of the enzyme ornithine carbamoyltransferase can result in severe CNS dysfunction or even in death, and identification of women at risk of being carriers of this genetic enzyme deficiency has been described.[1] The enzyme deficiency causes carbamoyl phosphate to accumulate, which stimulates the synthesis of orotidine. The test relies on giving a single dose of allopurinol, which will, in carriers, greatly increase the urinary excretion of orotidine. However, mutation analysis is now more usually used to establish the diagnosis.

1. Hauser ER, *et al.* Allopurinol-induced orotidinuria. *N Engl J Med* 1990; **322:** 1641–5. Correction. *ibid.* 1997; **336:** 1335.

Duchenne muscular dystrophy. Controlled studies of the use of allopurinol in an attempt to increase muscle ATP in Duchenne muscular dystrophy (p.1507) failed to show any benefit from treatment.[1-3]

1. Stern LM, *et al.* The progression of Duchenne muscular dystrophy: clinical trial of allopurinol therapy. *Neurology* 1981; **31:** 422–6.
2. Hunter JR, *et al.* Effects of allopurinol in Duchenne's muscular dystrophy. *Arch Neurol* 1983; **40:** 294–9.
3. Bertorini TE, *et al.* Chronic allopurinol and adenine therapy in Duchenne muscular dystrophy: effects on muscle function, nucleotide degradation, and muscle ATP and ADP content. *Neurology* 1985; **35:** 61–5.

Epilepsy. Reduction in the frequency of seizures has been described in some patients with severe or intractable epilepsy (p.465) when allopurinol was added to their existing antiepileptic therapy.[1-4] Although the mode of action was not known it was noted that the patients were not hyperuricaemic and that allopurinol did not affect plasma concentrations of existing antiepileptics.[1] However, others[5] have seen no benefit.

1. DeMarco P, Zagnoni P. Allopurinol and severe epilepsy. *Neurology* 1986; **36:** 1538–9.
2. Tada H, *et al.* Clinical effects of allopurinol on intractable epilepsy. *Epilepsia* 1991; **32:** 279–83.
3. Zagnoni PG, *et al.* Allopurinol as an add-on therapy in refractory epilepsy—a double-blind placebo-controlled randomised study. *Epilepsia* 1994; **35:** 107–12.
4. Togha M, *et al.* Allopurinol as adjunctive therapy in intractable epilepsy: a double-blind and placebo-controlled trial. *Arch Med Res* 2007; **38:** 313–16.
5. Coppola G, Pascotto A. Double-blind, placebo-controlled, crossover trial of allopurinol as add-on therapy in childhood refractory epilepsy. *Brain Dev* 1996; **18:** 50–2.

Organ and tissue transplantation. Allopurinol 25 mg on alternate days has been added to the immunosuppressive treatment for renal transplantation,[1] and is reported to reduce the frequency of acute rejection. One possible explanation for this effect is allopurinol's ability to suppress the production of free radicals (see Oxidative Stress, below). Organ and tissue transplantation, and the more usual drugs used in immunosuppressive regimens are discussed on p.1810. It should be noted that allopurinol interacts with azathioprine (see Immunosuppressants, under Interactions, above) and ciclosporin (p.1826).

1. Chocair P, *et al.* Low-dose allopurinol plus azathioprine/cyclosporin/prednisolone, a novel immunosuppressive regimen. *Lancet* 1993; **342:** 83–4.

Oxidative stress. Allopurinol, through its inhibition of xanthine oxidase, can block the development of superoxide free radicals during reperfusion after an ischaemic episode. Consequently, the ability of allopurinol to reduce oxidative stress has been investigated in a number of clinical situations.

In a small study[1] of patients with idiopathic dilated cardiomyopathy, short-term intracoronary allopurinol improved myocardial efficiency by decreasing the oxygen demand of left ventricular contraction.

In patients undergoing coronary artery bypass graft surgery, perioperative allopurinol reduced hospital mortality, the incidence of arrhythmias, the number of ischaemic events, and the need for inotropic support, although the findings were not consistent in all studies.[2]

Improved endothelial dysfunction has been found in patients with chronic heart failure given allopurinol.[3,4]

A large study[5] in neonates undergoing cardiac surgery found that allopurinol caused a reduction in seizures and cardiac events in those with hypoplastic left heart syndrome. No benefit was found in neonates with less severe forms of congenital heart disease, considered to be at lower risk of adverse surgical outcome or reperfusion injury. Allopurinol also failed to reduce the incidence of periventricular leucomalacia (thought to represent ischaemic infarction of the developing brain) in preterm infants compared with placebo in a large study.[6] Similarly, allopurinol did not reduce the incidence of infarct extension in patients with acute myocardial infarction.[7]

The possibility that allopurinol limits the production of free radicals has also led to allopurinol sodium being included as an ingredient of the University of Wisconsin solution [UW Solution; Belzer UW Solution (commercially available as *Viaspan*)], which is used for the preservation of organs for transplantation.[8]

A pilot study using allopurinol showed a beneficial effect on free radical formation, cerebral blood volume, and electrical brain activity in severely asphyxiated newborns.[9] However, a systematic review[10] of this and 2 other studies in such infants was unable to determine whether allopurinol produced clinically important benefits.

1. Cappola TP, *et al.* Allopurinol improves myocardial efficiency in patients with idiopathic dilated cardiomyopathy. *Circulation* 2001; **104:** 2407–11.
2. Weimert NA, *et al.* Allopurinol as a cardioprotectant during coronary artery bypass graft surgery. *Ann Pharmacother* 2003; **37:** 1708–11.
3. Doehner W, *et al.* Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricaemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation* 2002; **105:** 2619–24.
4. Farquharson CAJ, *et al.* Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation* 2002; **106:** 221–6.
5. Clancy RR, *et al.* Allopurinol neurocardiac protection trial in infants undergoing heart surgery using deep hypothermic circulatory arrest. *Pediatrics* 2001; **108:** 61–70.
6. Russell GAB, Cooke RWI. Randomised controlled trial of allopurinol prophylaxis in very preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1995; **73:** F27–F31.
7. Parmley LF, *et al.* Allopurinol therapy of ischemic heart disease with infarct extension. *Can J Cardiol* 1992; **8:** 280–6.
8. Southard JH, Belzer FO. Organ preservation. *Annu Rev Med* 1995; **46:** 235–47.
9. Van Bel F, *et al.* Effect of allopurinol on postasphyxial free radical formation, cerebral haemodynamics, and electrical brain activity. *Pediatrics* 1998; **101:** 185–93.
10. Chaudhari T, McGuire W. Allopurinol for preventing mortality and morbidity in newborn infants with suspected hypoxic-ischaemic encephalopathy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 14/07/08).

Prostatitis. Although allopurinol has been reported to be of benefit[1] in a small study in patients with chronic prostatitis (p.2181), a systematic review[2] found no other satisfactory evidence of benefit, and considered that the clinical relevance of the original study results was unclear.

1. Persson BE, *et al.* Ameliorative effect of allopurinol on nonbacterial prostatitis: a parallel double-blind controlled study. *J Urol (Baltimore)* 1996; **155:** 961–4.
2. McNaughton Collins M, Wilt T. Allopurinol for chronic prostatitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 18/05/06).

Protozoal infections. Allopurinol has been widely used as an adjunct to pentavalent antimonials in the treatment[1,2] of Old World *visceral leishmaniasis* (p.824), particularly where resistance to antimony alone is likely, although the degree of benefit has been called into question.[3] It has also been used with other drugs such as pentamidine[4] or azole antifungals[5-8], including in transplant patients[7] or those with AIDS,[5] or in whom antimonials were otherwise poorly tolerated.[8] Allopurinol has also been tried alone[9,10] or with other drugs in both Old World[11] and New World[12-14] *cutaneous* or *mucocutaneous leishmaniasis*; results, particularly in the latter, have been variable.

Some beneficial results have been noted[15-17] in indeterminate and chronic Chagas' disease (*American trypanosomiasis*, p.827), although it may be less effective than itraconazole.

The selective antiparasitic action of allopurinol is believed to be due to its incorporation into the protozoal, but not the mammalian, purine salvage pathway. This leads to the formation of 4-aminopyrazolopyrimidine ribonucleotide triphosphate, a highly toxic analogue of adenosine triphosphate, that is incorporated into ribonucleic acid. This action of allopurinol is shared by allopuri-

nol riboside, one of the minor metabolites in man, but not by oxipurinol, the major human metabolite. Thus, some studies have been conducted with allopurinol riboside, rather than allopurinol, in an attempt to enhance activity by avoiding host-mediated inactivation.[18]

1. di Martino L, *et al.* Low dosage combination of meglumine antimoniate plus allopurinol as first choice treatment of infantile visceral leishmaniasis in Italy. *Trans R Soc Trop Med Hyg* 1990; **84:** 534–5.
2. Gradoni L, *et al.* Treatment of Mediterranean visceral leishmaniasis. *Bull WHO* 1995; **73:** 191–7.
3. Singh NKP, *et al.* Combination therapy in kala-azar. *J Assoc Physicians India* 1995; **43:** 319–20.
4. Das VNR, *et al.* A randomized clinical trial of low dosage combination of pentamidine and allopurinol in the treatment of antimony unresponsive cases of visceral leishmaniasis. *J Assoc Physicians India* 2001; **49:** 609–13.
5. Raffi F, *et al.* Use of an itraconazole/allopurinol combination for the treatment of visceral leishmaniasis in a patient with AIDS. *Clin Infect Dis* 1995; **21:** 1338–9.
6. Torrus D, *et al.* Fluconazole plus allopurinol in treatment of visceral leishmaniasis. *J Antimicrob Chemother* 1996; **37:** 1042–3.
7. Hueso M, *et al.* The renal transplant patient with visceral leishmaniasis who could not tolerate meglumine antimoniate-cure with ketoconazole and allopurinol. *Nephrol Dial Transplant* 1999; **14:** 2941–3.
8. Kuyucu N, *et al.* Successful treatment of visceral leishmaniasis with allopurinol plus ketoconazole in an infant who developed pancreatitis caused by meglumine antimoniate. *Pediatr Infect Dis J* 2001; **20:** 455–7.
9. Halbert AR, *et al.* Allopurinol for Old World cutaneous leishmaniasis. *Pediatr Dermatol* 1995; **12:** 287–8.
10. D'Oliveira A, *et al.* Evaluating the efficacy of allopurinol for the treatment of cutaneous leishmaniasis. *Int J Dermatol* 1997; **36:** 938–40.
11. Esfandiarpour I, Alavi A. Evaluating the efficacy of allopurinol and meglumine antimoniate (Glucantime) in the treatment of cutaneous leishmaniasis. *Int J Dermatol* 2002; **41:** 521–4.
12. Velez I, *et al.* Inefficacy of allopurinol as monotherapy for Colombian cutaneous leishmaniasis: a randomized, controlled trial. *Ann Intern Med* 1997; **126:** 232–6.
13. Martinez S, *et al.* Treatment of cutaneous leishmaniasis with allopurinol and stibogluconate. *Clin Infect Dis* 1997; **24:** 165–9.
14. Llanos-Cuentas A, *et al.* Efficacy of sodium stibogluconate alone and in combination with allopurinol for treatment of mucocutaneous leishmaniasis. *Clin Infect Dis* 1997; **25:** 677–84.
15. Apt W, *et al.* Treatment of chronic Chagas' disease with itraconazole and allopurinol. *Am J Trop Med Hyg* 1998; **59:** 133–8.
16. Amato Neto V. Etiological treatment for infection by Trypanosoma cruzi. *Rev Inst Med Trop Sao Paulo* 1999; **41:** 211–3.
17. Apt W, *et al.* Itraconazole or allopurinol in the treatment of chronic American trypanosomiasis: the regression and prevention of electrocardiographic abnormalities during 9 years of follow-up. *Ann Trop Med Parasitol* 2003; **97:** 23–9.
18. Shapiro TA, *et al.* Pharmacokinetics and metabolism of allopurinol riboside. *Clin Pharmacol Ther* 1991; **49:** 506–14.

Renal calculi. In conjunction with a reduced dietary purine intake, high fluid intake, and potassium citrate, allopurinol may be used to prevent the recurrence of calcium oxalate renal calculi (p.2181) in patients with hyperuricosuria.[1,2] The recommended oral dose of allopurinol is 200 to 300 mg daily adjusted on the basis of subsequent 24-hour urinary urate excretion. Allopurinol is also advocated for the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones associated with deficient activity of the enzyme adenine phosphoribosyltransferase.

1. Ettinger B, *et al.* Randomized trial of allopurinol in the prevention of calcium oxalate calculi. *N Engl J Med* 1986; **315:** 1386–9.
2. Sorensen CM, Chandhoke PS. Hyperuricosuric calcium nephrolithiasis. *Endocrinol Metab Clin North Am* 2002; **31:** 915–25.

Sarcoidosis. Although corticosteroids remain the mainstay of drug therapy for sarcoidosis (p.1512), and other drugs are very much second line, there are reports[1-3] of benefit in cutaneous disease from the use of allopurinol.

1. Brechtel B, *et al.* Allopurinol: a therapeutic alternative for disseminated cutaneous sarcoidosis. *Br J Dermatol* 1996; **135:** 307–9.
2. Antony F, Layton AM. A case of cutaneous acral sarcoidosis with response to allopurinol. *Br J Dermatol* 2000; **142:** 1052–3.
3. Bregnhoej A, Jemec GB. Low-dose allopurinol in the treatment of cutaneous sarcoidosis: response in four of seven patients. *J Dermatol Treat* 2005; **16:** 125–7.

Schizophrenia. Involvement of purinergic neurotransmission has been hypothesised to play some role in schizophrenia (p.955), and allopurinol has been investigated as a possible adjunctive treatment, with some evidence of benefit, especially in patients with refractory positive symptoms.[1]

1. Buie LW, *et al.* Allopurinol as adjuvant therapy in poorly responsive or treatment refractory schizophrenia. *Ann Pharmacother* 2006; **40:** 2200–4.

Skin disorders. Reactive perforating collagenosis (RPC) is a condition in which altered collagen is eliminated through the epidermis; it may be inherited or acquired. In 3 of 4 patients with RPC refractory to antibacterials and oral and topical corticosteroids, significant improvement was seen with allopurinol, in terms of reduction of new lesions, improvement of existing lesions, and reduction of pruritus. The fourth patient died from unrelated causes before review.[1]

1. Hoque SR, *et al.* Acquired reactive perforating collagenosis: four patients with a giant variant treated with allopurinol. *Br J Dermatol* 2006; **154:** 759–62.

Preparations

BP 2008: Allopurinol Tablets;
USP 31: Allopurinol Oral Suspension; Allopurinol Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Alfadiman; Alloboxal†; Gotir†; Puritenk; ***Austral.:*** Allohexal; Allorin†; Allosig; Capurate†; Progout; Zyloprim; ***Austria:*** Allostad; Allotyrol†; Apurin†; Gewapurol; Gichtex; Purinol; Urosin; Zyloric; ***Belg.:*** Alpuric; Docallopu; Zyloric; ***Braz.:*** Labopurinol†; Lopurax; Uricemil†; Zilopur; Zyloric; ***Canad.:*** Novo-Purol; Zyloprim; ***Chile:*** Talol; Urogotan A; Zyloric; ***Cz.:*** Apurol†; Milurit; Purinol; ***Denm.:*** Abopur; Apurin; Hexanurat; ***Fin.:*** Allonol; Apurin; Arturic; Zyloric; ***Fr.:*** Zyloric; ***Ger.:*** Allo; Allo-Efeka; Allo-Puren†; Allobeta; Bleminol; Cellidrin; dura AL; Epidropal; Foligan; Jenapurinol; Milurit; Pureduct†; Remid; Uribenz; Uripurinol†; Zyloric; ***Gr.:*** Soluric; Zylapour; Zyloric; ***Hong Kong:*** Allnol†; Marinol; Mephanol†; Milurit; Progout; Zyloric; ***Hung.:*** Harpagin†; Milurit; ***India:*** Ciploric; Zyloric; ***Indon.:*** Algut; Benoxuric; Hycemia; Isoric; Licoric; Llanol; Nilapur; Pritanol; Puricemia; Reucid; Rinolic; Sinoric; Tylonic; Urica; Uricnol; Xanturic; Zyloric; ***Irl.:*** Purinol; Tipuric; Zyloric; ***Israel:*** Alloril; Zylol; Zyloric†; ***Ital.:*** Allurit; Uricemil†; Zyloric; ***Malaysia:*** Harpagin†; Uritab†; Zyloric; ***Mex.:*** Acyprin; Apo-Tinole†; Atisuril; Aurigen†; Bionol; Darzune; Etindrax; Unizuric; Zyloprim; ***Neth.:*** Apurin; Zyloric; ***Norw.:*** Allopur; Arturic; Zyloric; ***NZ:*** Allohexal; Allorin; Progout; ***Philipp.:*** Allurase; Alpurase; Elavil; Llanol; Lopric; Loricid; Purinase; Purispec; Puristen; Synol; Trianol; Xanurace; Zyloprim; ***Pol.:*** Allupol; Milurit; Zyloric; ***Port.:*** Alosfar; Uriprim; Zurim; Zyloric; ***Rus.:*** Purinol (Пуринол); ***S.Afr.:*** Lonol; Puricos; Redurate; Urinol; Zyloprim; ***Singapore:*** Erloric†; Progout; Valeric†; Zyloric; ***Spain:*** Zyloric; ***Swed.:*** Zyloric; ***Switz.:*** allo-basan†; Allopur; Cellidrine; Mephanol; Sigapurol N†; Uriconorme; Zyloric; ***Thai.:*** Alinol; Allopin; Apnol; Apurol; Loporic†; Medoric; Puricin†; Puride; Uricad; Valeric†; Xanol; Zyloric; ***Turk.:*** Allo-Urik; Allogut; Urikoliz; ***UK:*** Caplenal; Cosuric; Rimapurinol; Xanthomax†; Zyloric; ***USA:*** Aloprim; Zyloprim; ***Venez.:*** Aluprol†; Aluron; Zyloric.

Multi-ingredient: ***Arg.:*** Artrex; Colpuril; Xuric-A; ***Austria:*** Allobenz; Duovitan; Gichtex plus; ***Belg.:*** Comburic; ***Ger.:*** Allo.comp.; Allomaron†; Harpagin; ***Ital.:*** Uricodue; ***Philipp.:*** Allomaron; ***Port.:*** Acifugan†; ***S.Afr.:*** Allomaron†; ***Spain:*** Acifugan†; Facilit†; ***Thai.:*** Allomaron.

Benzbromarone *(BAN, USAN, rINN)*

Bensbromaron; Bentsbromaroni; Benzbromaron; Benzbromarona; Benzbromaronas; Benzbromaronum; L-2214; MJ-10061. 3,5-Dibromo-4-hydroxyphenyl 2-ethylbenzofuran-3-yl ketone.

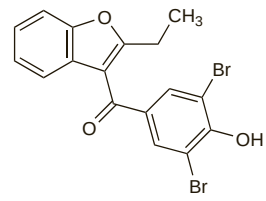
Бензбромарон

$C_{17}H_{12}Br_2O_3$ = 424.1.

CAS — 3562-84-3.

ATC — M04AB03.

ATC Vet — QM04AB03.



Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn*.

Ph. Eur. 6.2 (Benzbromarone). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

Adverse Effects

Benzbromarone may cause gastrointestinal adverse effects, especially diarrhoea. It may precipitate an acute attack of gout and cause uric acid renal calculi and renal colic. Hepatotoxicity has occurred and monitoring of liver function has been recommended.

Effects on the liver. Benzbromarone-induced liver damage has been reported.[1-4]

1. Van Der Klauw MM, *et al.* Hepatic injury caused by benzbromarone. *J Hepatol* 1994; **20:** 376–9.
2. Anonymous. Benzbromarone and hepatitis. *WHO Drug Inf* 2000; **14:** 29.
3. Wagayama H, *et al.* Fatal fulminant hepatic failure associated with benzbromarone. *J Hepatol* 2000; **32:** 874.
4. Arai M, *et al.* Fulminant hepatic failure associated with benzbromarone treatment: a case report. *J Gastroenterol Hepatol* 2002; **17:** 625–6.

Precautions

Benzbromarone should be avoided in patients with moderate or severe renal impairment, in those with uric acid renal calculi, and in those with urinary uric acid excretion rates of greater than 700 mg per 24 hours. Like other uricosurics, treatment with benzbromarone should not be started during an acute attack of gout. Similarly, an adequate fluid intake should be maintained to reduce the risk of uric acid renal calculi; additionally, alkalinisation of the urine may be considered.

Porphyria. Benzbromarone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

Aspirin and other salicylates antagonise the effect of benzbromarone. Benzbromarone may increase the anticoagulant activity of coumarin oral anticoagulants (see under Interactions of Warfarin, p.1429).

Antigout drugs. For mention of the effects of benzbromarone on the clearance of oxipurinol, the major active metabolite of *allopurinol*, and the view that this was not clinically significant, see under Interactions of Allopurinol, p.553.

Pharmacokinetics

Benzbromarone is only partially absorbed from the gastrointestinal tract, reaching peak plasma concentrations about 2 to 4 hours after an oral dose. Benzbromarone is extensively bound to plasma proteins. It is metabolised in the liver, and is excreted mainly in the faeces; a small amount appears in the urine.

◊ References.

1. Maurer H, Wollenberg P. Urinary metabolites of benzbromarone in man. *Arzneimittelforschung* 1990; **40:** 460–2.
2. Walter-Sack I, *et al.* Variation of benzbromarone elimination in man—a population study. *Eur J Clin Pharmacol* 1990; **39:** 173–6.

Uses and Administration

Benzbromarone is a uricosuric drug that reduces plasma concentrations of uric acid by blocking renal tubular reabsorption. It has been suggested that benzbromarone may also increase the intestinal elimination of uric acid. It has been used to treat hyperuricaemia including that associated with chronic gout (p.552) although it has been withdrawn in many countries due to reports of hepatotoxicity.

Benzbromarone is not used to treat acute attacks of gout and may exacerbate and prolong them if given during an attack; treatment should not start therefore until an acute attack has subsided.

The usual oral dose has been 50 to 200 mg daily. An NSAID or colchicine should be given initially to reduce the risk of precipitating acute gout. An adequate fluid intake should be maintained. Lower doses of benzbromarone (20 mg) have also been used in the form of a combination product with allopurinol.

◊ References.

1. Hanvivadhanakul P, *et al.* Efficacy of benzbromarone compared to allopurinol in lowering serum uric acid level in hyperuricemic patients. *J Med Assoc Thai* 2002; **85** (suppl 1): S40–S47.
2. Kumar S, *et al.* Benzbromarone therapy in management of refractory gout. *N Z Med J* 2005; **118:** U1528.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Max Uric†; ***Austria:*** Uricovac; ***Belg.:*** Desuric†; ***Braz.:*** Narcaricina†; ***Ger.:*** Narcaricin†; ***Hung.:*** Harpagin†; ***Jpn:*** Urinorm; ***Malaysia:*** Harpagin†; ***Mex.:*** Desuric†; ***Neth.:*** Desuric; ***S.Afr.:*** Minuric†; ***Singapore:*** Narcaricin†; ***Spain:*** Urinorm; ***Switz.:*** Desuric†; Obaron†; ***Thai.:*** Narcaricin†.

Multi-ingredient: ***Austria:*** Allobenz; Duovitan; Gichtex plus; ***Belg.:*** Comburic; ***Ger.:*** Allo.comp.; Allomaron†; Harpagin; ***Philipp.:*** Allomaron; ***Port.:*** Acifugan†; ***S.Afr.:*** Allomaron†; ***Spain:*** Acifugan†; Facilit†; ***Thai.:*** Allomaron.

Benziodarone *(BAN, rINN)*

Benciodarona; Bentsiodaroni; Benziodaron; Benziodaronum; L-2329. 2-Ethylbenzofuran-3-yl 4-hydroxy-3,5-di-iodophenyl ketone.

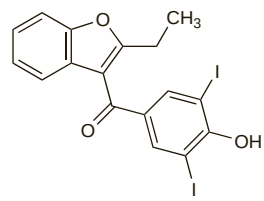
Бензйодарон

$C_{17}H_{12}I_2O_3$ = 518.1.

CAS — 68-90-6.

ATC — C01DX04.

ATC Vet — QC01DX04.



Profile

Benziodarone is a uricosuric drug structurally related to benzbromarone (see above) that has been given orally to reduce hyperuricaemia in chronic gout.

Benziodarone has been associated with jaundice and thyroid disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Spain: Dilafurane†.

Multi-ingredient: ***Ital.:*** Uricodue.