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.

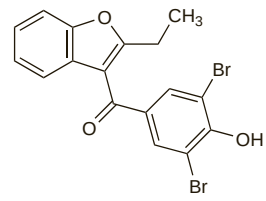
Бензбромарон

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

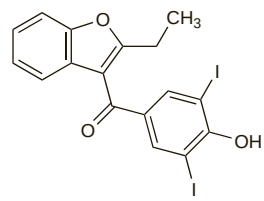
Бензйодарон

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