Voriconazole *(BAN, USAN, rINN)*

UK-109496; Voriconazol; Voriconazolum; Vorikonazol. (2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol.

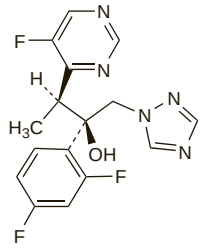
Вориконазол

$C_{16}H_{14}N_5F_3O$ = 349.3.

CAS — 137234-62-9.

ATC — J02AC03.

ATC Vet — QJ02AC03.



Adverse Effects

The most commonly reported adverse effects with voriconazole are visual disturbances, fever, rashes, nausea, vomiting, diarrhoea, abdominal pain, headache, sepsis, respiratory disorders, and peripheral oedema. There have been some serious hepatic reactions including fatalities. Skin reactions have included rare cases of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Photosensitivity reactions may occur and are more likely during long-term treatment.

Other adverse effects reported as being common during treatment with voriconazole include: chills, flu-like syndrome, asthenia, back pain, chest pain, injection site reactions, facial oedema, hypotension, sinusitis, altered liver function tests, jaundice, cheilitis, blood disorders, hypokalaemia, hypoglycaemia, dizziness, hallucinations, confusion, depression, anxiety, tremor, agitation, paraesthesia, pruritus, alopecia, exfoliative dermatitis, acute renal failure, and haematuria. Hypersensitivity reactions, including anaphylaxis, have occurred rarely.

Effects on the blood. Fever and leucocytosis with eosinophilia in one patient has been attributed to voriconazole treatment.[1]

1. Vishnubhotla P, *et al.* Fever and eosinophilia associated with voriconazole. *Ann Pharmacother* 2004; **38:** 900–901.

Effects on the heart. Bradycardia with a prolonged QT interval and asymptomatic episodes of torsade de pointes occurred in a 15-year-old patient, after 3 weeks of voriconazole therapy at usual doses.[1] All drug treatment was stopped but the effects recurred on rechallenge with a small dose of voriconazole.

1. Alkan Y, *et al.* Voriconazole-induced QT interval prolongation and ventricular tachycardia: a non-concentration-dependent adverse effect. *Clin Infect Dis* 2004; **39:** e49–e52.

Effects on mental function. There have been reports[1,2] of patients experiencing hallucinations (auditory or visual) during treatment with voriconazole. In one study 18 of 415 patients (4.3%) given voriconazole had visual hallucinations compared with 2 of 422 (0.5%) given amphotericin B.[1]

1. Walsh TJ, *et al.* Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002; **346:** 225–34.
2. Agrawal AK, Sherman LK. Voriconazole-induced musical hallucinations. *Infection* 2004; **32:** 293–5.

Precautions

Acute renal failure may occur with voriconazole and renal function should be monitored during treatment. Liver function should also be monitored before and during treatment with voriconazole. It should be used with caution in patients with hepatic impairment and doses may need to be adjusted (see under Uses and Administration, below). Patients should avoid sunlight during treatment as photosensitivity reactions have been reported. Visual disturbances may occur and patients affected should not drive or operate hazardous machinery. In addition, all patients, whether affected by visual disturbances or not, should not drive at night, and should have their visual function monitored if they are receiving voriconazole for more than 28 days. Voriconazole has been associated with QT interval prolongation and should therefore be given with caution to patients with potentially pro-arrhythmic conditions.

Voriconazole has been shown to be teratogenic and embryotoxic in *animal* studies and its use is generally not recommended during pregnancy. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532. Licensed product information recommends that women of child-bearing potential should use effective contraception during treatment with voriconazole.

Interactions

Voriconazole is metabolised by cytochrome P450 isoenzymes CYP2C19, CYP2C9, and CYP3A4. Use of drugs that either inhibit or induce these isoenzymes may increase or decrease plasma concentrations of voriconazole, respectively. Rifampicin has been shown to decrease voriconazole plasma concentrations and a similar effect may be expected with carbamazepine or phenobarbital; use of voriconazole with these drugs is therefore not recommended.

Concentrations of other drugs that are metabolised by CYP2C19, CYP2C9, or CYP3A4 may be increased by voriconazole. Increased plasma concentrations of astemizole, cisapride, pimozide, quinidine, and terfenadine could be expected and concomitant use is contra-indicated because of the risk of cardiac arrhythmias including torsade de pointes. Use with ergot alkaloids such as ergotamine and dihydroergotamine is also contra-indicated because of the possible risk of ergotism. Increased plasma concentrations of sirolimus and tacrolimus have been noted; use with sirolimus is contra-indicated, although tacrolimus may be used providing its dose is reduced and concentrations monitored. Similarly, reduced dose with monitoring is recommended for ciclosporin. Likewise, monitoring and possible dose reductions of methadone are recommended during concomitant use. Concentrations of oral anticoagulants may be affected and increased prothrombin time has occurred with warfarin; monitoring should therefore be carried out. Close monitoring of blood glucose is necessary if voriconazole is used with oral hypoglycaemics such as the sulfonylureas. Dose reductions may be needed for some statins, calcium-channel blockers, vinca alkaloids, and some benzodiazepines (such as midazolam and triazolam) if their plasma concentrations are increased.

Interactions may occur where both voriconazole and the other drug are affected. Examples are phenytoin and rifabutin (where concentrations of voriconazole are reduced but those of phenytoin or rifabutin are increased). If it is essential to give either drug with voriconazole, then an increase in the dose of voriconazole is recommended. With omeprazole, the plasma concentration of both drugs may be increased and a reduced dose of omeprazole is recommended.

Voriconazole may inhibit metabolism of non-nucleoside reverse transcriptase inhibitors and they in turn may either inhibit the metabolism of voriconazole (e.g. delavirdine and efavirenz) or induce the metabolism of voriconazole (e.g. efavirenz and nevirapine). Co-administration of voriconazole and efavirenz is contra-indicated. Similarly, voriconazole may inhibit metabolism of HIV-protease inhibitors (e.g. saquinavir, amprenavir, and nelfinavir) while they may in turn inhibit the metabolism of voriconazole. High doses of ritonavir (400 mg twice daily) significantly decrease plasma concentrations of voriconazole and co-administration is contra-indicated. Similar effects have been seen with low doses of ritonavir (100 mg twice daily) and use with voriconazole should be avoided where possible. Indinavir, however, does not appear to interact with voriconazole.

For further information on interactions between drugs metabolised by the cytochrome P450 isoenzyme CYP3A and azoles, see under Itraconazole, p.537.

◊ For reviews of drug interactions with azole antifungals, see Itraconazole, p.537.

Antimicrobial Action

Voriconazole is a triazole antifungal that in sensitive fungi inhibits cytochrome P450-dependent enzymes resulting in the impairment of ergosterol synthesis in fungal cell membranes. Voriconazole has a broad spectrum of activity against all *Candida* species, including fluconazole-resistant strains, as well as *Aspergillus* spp., *Scedosporium* spp., and *Fusarium* spp.

◊ Reports of breakthrough zygomycosis and other fungal infections in immunocompromised patients treated empirically or prophylactically with voriconazole.[1-5]

1. Marty FM, *et al.* Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. *N Engl J Med* 2004; **350:** 950–2.
2. Siwek GT, *et al.* Invasive zygomycosis in hematopoietic stem cell transplant recipients receiving voriconazole prophylaxis. *Clin Infect Dis* 2004; **39:** 584–7.
3. Imhof A, *et al.* Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. *Clin Infect Dis* 2004; **39:** 743–6.
4. Oren I. Breakthrough zygomycosis during empirical voriconazole therapy in febrile patients with neutropenia. *Clin Infect Dis* 2005; **40:** 770–1.
5. Vigouroux S, *et al.* Zygomycosis after prolonged use of voriconazole in immunocompromised patients with hematologic disease: attention required. *Clin Infect Dis* 2005; **40:** e35-e37.

Pharmacokinetics

Voriconazole exhibits non-linear pharmacokinetics due to saturable metabolism. It is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 1 to 2 hours after an oral dose. Plasma protein binding of voriconazole is about 58%. Voriconazole diffuses into CSF.

Voriconazole is metabolised by hepatic cytochrome P450 isoenzyme CYP2C19; the major metabolite is the inactive *N*-oxide. Metabolism via isoenzymes CYP2C9 and CYP3A4 has also been demonstrated *in vitro*. About 80% of voriconazole is excreted in the urine.

◊ References.

1. Purkins L, *et al.* Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. *Antimicrob Agents Chemother* 2002; **46:** 2546–53.
2. Johnston A. The pharmacokinetics of voriconazole. *Br J Clin Pharmacol* 2003; **56** (suppl 1): 1.
3. Walsh TJ, *et al.* Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. *Antimicrob Agents Chemother* 2004; **48:** 2166–72.
4. Theuretzbacher U, *et al.* Pharmacokinetic/pharmacodynamic profile of voriconazole. *Clin Pharmacokinet* 2006; **45:** 649–63.

Uses and Administration

Voriconazole is a triazole antifungal used mainly in immunocompromised patients for the treatment of invasive aspergillosis (p.517), candidaemia (p.518) in non-neutropenic patients, fluconazole-resistant serious invasive candidiasis, oesophageal candidiasis, and serious fungal infections due to *Scedosporium* and *Fusarium* spp.

Voriconazole may be given orally or intravenously.

Oral doses as film-coated tablets should be taken at least 1 hour before, or 1 hour after, a meal; oral suspensions should be taken at least 1 hour before, or 1 to 2 hours after, a meal. The oral suspension may be preferred in children.

The following ***oral loading doses*** of voriconazole are given every 12 hours for the first 24 hours:

- adults and adolescents weighing more than 40 kg: 400 mg
- under 40 kg: 200 mg
- children aged 2 to 12 years: no loading dose

Subsequent ***oral maintenance doses*** are:

- adults and adolescents over 40 kg: 200 mg twice daily, increased to 300 mg twice daily if the response is inadequate
- under 40 kg: 100 mg twice daily, increased to 150 mg twice daily if the response is inadequate
- children aged 2 to 12 years: 200 mg twice daily

US licensed product information does not suggest a loading dose for oesophageal candidiasis; oral maintenance doses are as above and treatment should be given for a minimum of 14 days and continued for at least 7 days after resolution of symptoms.

Intravenous loading doses of voriconazole are:

- adults and adolescents: 6 mg/kg every 12 hours for the first 24 hours
- children aged 2 to 12 years: no loading dose

Intravenous maintenance doses are:

- adults and adolescents: 4 mg/kg twice daily; a lower dose of 3 mg/kg twice daily may be suitable for candidaemia in non-neutropenic patients or for deep tissue *Candida* infections, or for patients unable to tolerate the higher dose
- children aged 2 to 12 years: 7 mg/kg twice daily; 4 mg/kg twice daily may be used in those unable to tolerate the higher dose

Intravenous infusions should be given at a maximum rate of 3 mg/kg per hour over 1 to 2 hours. UK licensed product information recommends that intravenous therapy should not be given for longer than 6 months.

Doses of voriconazole should be modified in patients with hepatic or renal impairment (see below). For a suggested dose in patients taking the NNRTI efavirenz see Interactions, Antifungals, p.873.

◊ Reviews.

1. Muijsers RBR, *et al.* Voriconazole: in the treatment of invasive aspergillosis. *Drugs* 2002; **62:** 2655–64.
2. Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. *Clin Infect Dis* 2003; **36:** 630–7.
3. Pearson MM, *et al.* Voriconazole: a new triazole antifungal agent. *Ann Pharmacother* 2003; **37:** 420–32.
4. Gothard P, Rogers TR. Voriconazole for serious fungal infections. *Int J Clin Pract* 2004; **58:** 74–80.
5. Donnelly JP, De Pauw BE. Voriconazole—a new therapeutic agent with an extended spectrum of antifungal activity. *Clin Microbiol Infect* 2004; **10** (suppl 1): 107–17.
6. Scott LJ, Simpson D. Voriconazole: a review of its use in the management of invasive fungal infections. *Drugs* 2007; **67:** 269–98.

Administration in hepatic impairment. No dosage adjustment is necessary when voriconazole is given to patients with acute hepatic impairment but doses should be modified in patients with chronic disease. Patients with mild to moderate hepatic cirrhosis (Child-Pugh category A and B) should receive the standard loading doses of voriconazole (see above) but maintenance doses should be halved. Doses for patients with severe hepatic cirrhosis (Child-Pugh category C) have not been established.

Administration in renal impairment. No dose adjustment is needed for oral voriconazole in patients with renal impairment. Patients with a creatinine clearance less than 50 mL/minute should receive oral voriconazole instead of intravenous voriconazole, as accumulation of the intravenous vehicle, sulfobutyl ether beta-cyclodextrin sodium (SBECD), may occur. When intravenous voriconazole is considered justified in such patients, serum creatinine should be closely monitored and consideration given to changing to the oral route if increases occur.

Although voriconazole is haemodialysed, no dose adjustment is required for patients on haemodialysis.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Vfend; ***Austral.:*** Vfend; ***Austria:*** Vfend; ***Belg.:*** Vfend; ***Braz.:*** Vfend; ***Canad.:*** Vfend; ***Chile:*** Vfend; ***Cz.:*** Vfend; ***Denm.:*** Vfend; ***Fin.:*** Vfend; ***Fr.:*** Vfend; ***Ger.:*** Vfend; ***Gr.:*** Vfend; ***Hong Kong:*** Vfend; ***Hung.:*** Vfend; ***Indon.:*** Vfend; ***Irl.:*** Vfend; ***Israel:*** Vfend; ***Ital.:*** Vfend; ***Malaysia:*** Vfend; ***Mex.:*** Vfend; ***Neth.:*** Vfend; ***Norw.:*** Vfend; ***NZ:*** Vfend; ***Pol.:*** Vfend; ***Port.:*** Vfend; ***S.Afr.:*** Vfend; ***Singapore:*** Vfend; ***Spain:*** Vfend; ***Swed.:*** Vfend; ***Switz.:*** Vfend; ***Thai.:*** Vfend; ***UK:*** Vfend; ***USA:*** Vfend; ***Venez.:*** Vorcum.

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.

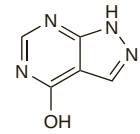
Аллопуринол

$C_5H_4N_4O$ = 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.