Interactions

Posaconazole is metabolised by the uridine diphosphate glucuronosyltransferase UGT1A4, and is a substrate for p-glycoprotein. The use of drugs that either inhibit (for example, clarithromycin, erythromycin, ciclosporin, and verapamil) or induce (see below) enzymes in this pathway may increase or decrease plasma-posaconazole concentrations, respectively. Rifabutin and phenytoin have been shown to decrease plasma-posaconazole concentrations and a similar effect may be expected with rifampicin, carbamazepine, primidone, and phenobarbital. Concentrations of posaconazole are reduced by cimetidine possibly due to reduced absorption of posaconazole as a result of decreased acid production and reduced posaconazole concentrations may also be expected with other H_2-antagonists and proton pump inhibitors.

Posaconazole is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 and concentrations of other drugs that are metabolised by this enzyme pathway may be increased by posaconazole. Increased plasma concentrations of astemizole, cisapride, halofantrine, 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. HMG-CoA reductase inhibitors such as atorvastatin, lovastatin, and simvastatin are contra-indicated as concomitant use as been associated with rhabdomyolysis. Increased plasma concentrations of sirolimus and tacrolimus have been noted; doses of sirolimus and tacrolimus may need to be reduced and concentrations monitored. Similarly, dose reduction with monitoring is recommended for ciclosporin. Close monitoring of blood glucose is necessary if posaconazole is used with oral hypoglycaemics such as the sulfonylureas. Dose reductions may be needed for calcium-channel blockers, digoxin, vinca alkaloids, and some benzodiazepines (such as alprazolam, midazolam, and triazolam). It is expected that posaconazole will increase the concentrations of HIV-protease inhibitors and NNRTIs.

Interactions may occur where both posaconazole and the other drug are affected. Examples are ciclosporin (where concentrations of both posaconazole and ciclosporin are increased) and rifabutin (where concentrations of posaconazole are reduced but those of rifabutin are increased).

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

Posaconazole is a triazole antifungal drug that in sensitive fungi inhibits the enzyme lanosterol 14α-demethylase (CYP51) resulting in the impairment of ergosterol synthesis in fungal cell membranes. Posaconazole has activity against *Candida* spp., *Aspergillus* spp., *Coccidioides immitis*, *Fonsecaea pedrosoi*, and some species of *Fusarium* and zygomycetes.

Pharmacokinetics

Posaconazole exhibits linear pharmacokinetics after single and multiple doses with a high fat meal. No further increases in plasma concentration are seen with doses above 800 mg daily. It is slowly absorbed from the gastrointestinal tract and has a large volume of distribution. Peak plasma concentrations occur about 5 hours after an oral dose. Steady state plasma-posaconazole concentrations occur after 7 to 10 days of multiple dosage. Plasma protein binding is over 98%.

Metabolism plays only a minor role in the elimination of posaconazole; most circulating metabolites are glucuronide conjugates with only small amounts of oxidative metabolites. Posaconazole is slowly eliminated with a mean elimination half-life of 35 hours. The main elimination route of posaconazole is via the faeces (77%) where 66% of a dose is excreted unchanged. About 14% of a dose is excreted in the urine with only trace amounts excreted unchanged.

◊ Reviews.

1. Courtney R, *et al.* Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. *Antimicrob Agents Chemother* 2003; **47:** 2788–95.

Uses and Administration

Posaconazole is an oral triazole antifungal used in the treatment of severe oropharyngeal candidiasis. It is also indicated in the treatment of invasive aspergillosis, chromoblastomycosis, coccidioidomycosis, fusariosis, or mycetoma infections in patients who are resistant to, or intolerant of, other antifungals. Posaconazole is also given for the prophylaxis of fungal infections in patients who are at high risk for invasive fungal disease due to prolonged neutropenia.

Posaconazole is given orally as a suspension; doses should be given with a meal, or a nutritional supplement in those who cannot tolerate food, in order to enhance oral absorption and ensure adequate exposure.

For the treatment of **oropharyngeal candidiasis** posaconazole is given in a loading dose of 200 mg on the first day, followed by 100 mg daily for 13 days. In patients with oropharyngeal candidiasis refractory to itraconazole and/or fluconazole, posaconazole is given at a dose of 400 mg twice daily.

In patients with refractory **invasive systemic fungal infections**, it is given at a dose of 400 mg twice daily. Patients not tolerating food or nutritional supplements should take 200 mg four times daily.

In the **prophylaxis** of invasive fungal infections, the recommended dose is 200 mg three times daily. Treatment is continued until recovery from neutropenia or immunosuppression. In patients undergoing cytotoxic chemotherapy for haematological malignancies, or haematopoietic stem-cell transplantation, treatment should begin several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells/mm^3.

◊ References.

1. Herbrecht R. Posaconazole: a potent, extended-spectrum triazole anti-fungal for the treatment of serious fungal infections. *Int J Clin Pract* 2004; **58:** 612–24.
2. Segal BH, *et al.* Posaconazole as salvage therapy in patients with chronic granulomatous disease and invasive filamentous fungal infection. *Clin Infect Dis* 2005; **40:** 1684–8.
3. Keating GM. Posaconazole. *Drugs* 2005; **65:** 1553–67.
4. Raad II, *et al.* Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. *Clin Infect Dis* 2006; **42:** 1726–34.
5. Nagappan V, Deresinski S. Posaconazole: a broad-spectrum triazole antifungal agent. *Clin Infect Dis* 2007; **45:** 1610–7.
6. Frampton JE, Scott LJ. Posaconazole : a review of its use in the prophylaxis of invasive fungal infections. *Drugs* 2008; **68:** 993–1016.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Noxafil; ***Cz.:*** Noxafil; ***Fr.:*** Noxafil; ***Gr.:*** Noxafil; ***Neth.:*** Noxafil; ***NZ:*** Noxafil; ***Pol.:*** Noxafil; ***Swed.:*** Noxafil; ***UK:*** Noxafil; ***USA:*** Noxafil.

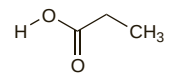
Propionic Acid

E280; E283 (potassium propionate); Kwas propionowy; Propanoico, ácido. Propanoic acid.

Пропионовая Кислота

$C_2H_5.CO_2H$ = 74.08.

CAS — 79-09-4.



Pharmacopoeias. In *Fr.* Also in *USNF.*

USNF 26 (Propionic Acid). An oily liquid having a slight pungent, rancid odour. Miscible with water, with alcohol, and with various other organic solvents. Store in airtight containers.

Calcium Propionate

E282. Calcium propanoate.

Пропионат Кальция

$(C_3H_5O_2)_2Ca$ = 186.2.

CAS — 4075-81-4 (anhydrous calcium propionate); 56744-45-7 (calcium propionate monohydrate).

Sodium Propionate

E281; Natrii propionas; Natrio propionatas; Natriumpropionaatti; Natriumpropionat; Nátrium-propionát; Propionan sodný; Propionato de sodio; Sodium, propionate de. Sodium propanoate.

Пропионат Натрия

$C_3H_5NaO_2$ = 96.06.

CAS — 137-40-6 (anhydrous sodium propionate); 6700-17-0 (sodium propionate hydrate).

ATC — S01AX10.

ATC Vet — QA16QA02; QS01AX10.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Sodium Propionate). Slightly hygroscopic colourless crystals or white or almost white powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 7.8 to 9.2. Store in airtight containers.

USNF 26 (Sodium Propionate). Colourless transparent crystals or a granular crystalline powder; odourless or with a faint acetic-butyric odour. Deliquescent in moist air. Soluble 1 in 1 of water, 1 in 0.65 of boiling water, and 1 in 24 of alcohol; practically insoluble in chloroform and in ether. Store in airtight containers.

Profile

Propionic acid and its salts are antifungals. Calcium and sodium propionate have been used topically, usually with other antimicrobials for the treatment of dermatophyte infections. Eye drops containing sodium propionate have also been used.

Propionic acid and its calcium, sodium, and potassium salts are used in the baking industry as inhibitors of moulds.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Propionat.

Multi-ingredient: ***Arg.:*** Cicatrol; Farm-X; Fungicida†; Hipoglos Cicatrizante; Novo Miconol; Piecidex†; Plusderm†; ***Austral.:*** Mycoderm; ***Austria:*** Dermowund; ***Braz.:*** Andriodermol; Colpagex N; Gynax-N; Micotox†; Vagitrin-N; ***Canad.:*** Amino-Cerv; ***Chile:*** Fittig; ***Fr.:*** Dermacide; Otoralgyl a la phenylephrine†; ***Hong Kong:*** Mycoderm; ***Indon.:*** Decyline; ***Israel:*** Otomycin; ***Malaysia:*** Mycoderm; ***S.Afr.:*** Neopan; ***USA:*** Amino-Cerv; Prophyllin; ***Venez.:*** Diodonato†.

Pyrrolnitrin *(USAN, rINN)*

52230; NSC-107654; Pirrolnitrina; Pyrrolnitrine; Pyrrolnitrinum. 3-Chloro-4-(3-chloro-2-nitrophenyl)pyrrole.

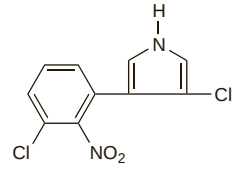
Пирролнитрин

$C_{10}H_6Cl_2N_2O_2$ = 257.1.

CAS — 1018-71-9.

ATC — D01AA07.

ATC Vet — QD01AA07.



Pharmacopoeias. In *Jpn.*

Profile

Pyrrolnitrin is an antifungal antibiotic isolated from *Pseudomonas pyrrocinia* and applied topically in the treatment of superficial fungal infections.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Micutrin.

Multi-ingredient: ***Ital.:*** Micutrin Beta†; ***Port.:*** Pirrolfungin†.
