Amorolfine *(BAN, USAN, rINN)*

Amorolfiini; Amorolfin; Amorolfina; Amorolfinum; Ro-14-4767/000. (±)-*cis*-2,6-Dimethyl-4-[2-methyl-3-(*p*-*tert*-pentylphenyl)propyl]morpholine.

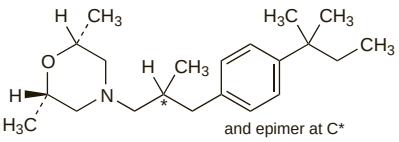
Аморольфин

$C_{21}H_{35}NO$ = 317.5.

CAS — 78613-35-1.

ATC — D01AE16.

ATC Vet — QD01AE16.



Amorolfine Hydrochloride *(BANM, rINNM)*

Amorolfine, Chlorhydrate d'; Amorolfini Hydrochloridum; Hidrocloruro de amorolfina; Ro-14-4767/002.

Аморольфина Гидрохлорид

$C_{21}H_{35}NO,HCl$ = 354.0.

CAS — 78613-38-4.

ATC — D01AE16.

ATC Vet — QD01AE16.

Adverse Effects

Skin irritation, presenting as erythema, pruritus, or a burning sensation, and, rarely, more severe skin reactions have been reported after topical application of amorolfine.

Antimicrobial Action

Amorolfine is a morpholine derivative with antifungal activity. It appears to act by interfering with the synthesis of sterols essential for the functioning of fungal cell membranes.

Amorolfine is active *in vitro* against a wide variety of pathogenic and opportunistic fungi including dermatophytes, *Blastomyces dermatitidis*, *Candida* spp., *Histoplasma capsulatum*, and *Sporothrix schenckii*. It also has variable activity against *Aspergillus* spp. However, despite its *in vitro* activity, amorolfine is inactive when given systemically and this limits its use to topical application for superficial infections.

Uses and Administration

Amorolfine is a morpholine derivative applied topically as the hydrochloride in the treatment of fungal nail and skin infections (p.521). After topical application, systemic absorption of amorolfine is negligible.

For the treatment of nail infections caused by dermatophytes, yeasts, and moulds a lacquer containing the equivalent of 5% amorolfine is painted onto the affected nail once or sometimes twice weekly until the nail has regenerated. Treatment generally needs to be continued for 6 to 12 months.

For skin infections, including dermatophyte infections, a cream containing the equivalent of 0.25% amorolfine is applied once daily for at least 2 to 3 weeks (up to 6 weeks for foot infections) and continued for 3 to 5 days after clinical cure is achieved.

◊ Reviews.

1. Haria M, Bryson HM. Amorolfine: a review of its pharmacological properties and therapeutic potential in the treatment of onychomycosis and other superficial fungal infections. *Drugs* 1995; **49:** 103–20.
2. Flagothier C, *et al.* New insights into the effect of amorolfine nail lacquer. *Mycoses* 2005; **48:** 91–4.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Loceryl; Locetar†; Micocide A; ***Austral.:*** Loceryl; ***Austria:*** Loceryl; ***Belg.:*** Loceryl; ***Braz.:*** Loceryl; ***Chile:*** Loceryl; ***Cz.:*** Loceryl; ***Denm.:*** Loceryl; ***Fin.:*** Loceryl; ***Fr.:*** Loceryl; ***Ger.:*** Loceryl; ***Gr.:*** Loceryl; ***Hong Kong:*** Loceryl; ***Hung.:*** Loceryl; ***Irl.:*** Loceryl; ***Ital.:*** Locetar; ***Jpn:*** Pekiron; ***Malaysia:*** Loceryl; ***Mex.:*** Loceryl; ***Norw.:*** Loceryl; ***NZ:*** Loceryl; ***Philipp.:*** Locetar; ***Pol.:*** Loceryl; ***Port.:*** Locetar; ***Rus.:*** Loceryl (Лоцерил); ***S.Afr.:*** Loceryl; ***Singapore:*** Loceryl; ***Spain:*** Locetar; Odenil; ***Swed.:*** Loceryl; ***Switz.:*** Loceryl; ***UK:*** Curanail; Loceryl; ***Venez.:*** Loceryl.

Amphotericin B *(BANM, rINN)*

Amfotericin; Amfotericin B; Amfotericina B; Amfotericinas B; Amforterisiini; Amforterisiini B; Amforterisin; Amforterisin B; Amfoterycyna b; Amphotericin; Amphotéricine B; Amphotericinum; Amphotericinum B; Anfotericina B.

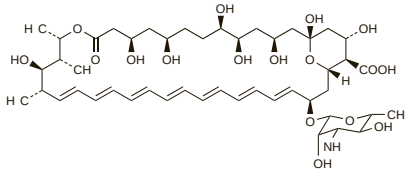
Амфотерицин В

$C_{47}H_{73}NO_{17}$ = 924.1.

CAS — 1397-89-3.

ATC — A01AB04; A07AA07; G01AA03; J02AA01.

ATC Vet — QA01AB04; QA07AA07; QG01AA03; QJ02AA01.



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

Ph. Eur. 6.2 (Amphotericin B; Amphotericin BP 2008). A mixture of antifungal polyenes produced by the growth of certain strains of *Streptomyces nodosus* or by any other means. It consists largely of amphotericin B. It occurs as a yellow or orange powder. The potency is not less than 750 units per mg with reference to the dried substance. It contains not more than 10% of tetraenes, or not more than 5% if intended for use in parenteral dosage forms. Practically insoluble in water and in alcohol; soluble in dimethyl sulfoxide and in propylene glycol; slightly soluble in dimethylformamide; very slightly soluble in methyl alcohol. Amphotericin B is inactivated at low pH values. Store at 2° to 8° in airtight containers. Protect from light.

USP 31 (Amphotericin B). A yellow to orange, odourless or practically odourless, powder. It contains not less than 750 micrograms of $C_{47}H_{73}NO_{17}$ per mg, and, for material intended for oral or topical use, not more than 15% of amphotericin A, both calculated on the dried substance. Insoluble in water, in dehydrated alcohol, in ether, in benzene, and in toluene; soluble in dimethylformamide, in dimethyl sulfoxide, and in propylene glycol; slightly soluble in methyl alcohol. Store at a temperature not exceeding 8° in airtight containers. Protect from light.

◊ References.

1. Kintzel PE, Smith GH. Practical guidelines for preparing and administering amphotericin B. *Am J Hosp Pharm* 1992; **49:** 1156–64.

Formulation. Conventional formulations of amphotericin B injection are typically a complex of amphotericin B and deoxycholate with suitable buffers which form a colloidal dispersion when reconstituted. Nonconventional '**lipid**' formulations of amphotericin B for injection include liposomal amphotericin B, a colloidal dispersion of an amphotericin B and sodium cholesteryl sulfate complex, and a phospholipid complex.

Incompatibility. Because of the wide range of incompatibilities reported with conventional and lipid formulations of amphotericin B, it is generally advisable not to mix them with any other drug. Most incompatibilities are caused by precipitation of amphotericin B due to a change in pH or by the disruption of the colloidal suspension. Precipitation can occur if amphotericin B is added to sodium chloride 0.9% or to electrolyte solutions.

Although heparin is generally reported to be compatible with conventional amphotericin B injection, care should be taken if heparin flush solutions, which are diluted with sodium chloride solution, are used to maintain the patency of intravenous lines in patients receiving amphotericin B. Flushing the intravenous line with 5% glucose solution has been suggested.

Mixtures of conventional amphotericin B in commercial lipid emulsions have been reported to be unstable,[1-3] although others have reported satisfactory stability.[4-6] In one study,[6] vigorous agitation of the mixtures enhanced their stability when compared with gentle mixing.

1. Ericsson O, *et al.* Amphotericin B is incompatible with lipid emulsions. *Ann Pharmacother* 1996; **30:** 298.
2. Ranchère JY, *et al.* Amphotericin B intralipid formulation: stability and particle size. *J Antimicrob Chemother* 1996; **37:** 1165–9.
3. Heide PE. Precipitation of amphotericin B from iv fat emulsion. *Am J Health-Syst Pharm* 1997; **54:** 1449.
4. Lopez RM, *et al.* Stability of amphotericin B in an extemporaneously prepared iv fat emulsion. *Am J Health-Syst Pharm* 1996; **53:** 2724–7.
5. Owens D, *et al.* Stability of amphotericin B 0.05 and 0.5 mg/mL in 20% fat emulsion. *Am J Health-Syst Pharm* 1997; **54:** 683–6.
6. Shadkhan Y, *et al.* The use of commercially available lipid emulsions for the preparation of amphotericin B-lipid admixtures. *J Antimicrob Chemother* 1997; **39:** 655–8. Correction. *ibid.* 1998; **42:** 413.

Preparation of solutions for injection. Recommendations from the manufacturers for preparation of amphotericin solutions are:

- *conventional amphotericin B* formulations for injection are prepared by reconstitution of amphotericin B with sterile water for injection without preservatives, then dilution with glucose injection 5% with a pH above 4.2 to the desired final concentration.
- *liposomal amphotericin B*: injections are prepared by reconstitution with sterile water for injection without a preservative; the required reconstituted amount is then withdrawn and injected via a sterile filter into the desired volume of glucose 5%.
- *amphotericin B-sodium cholesteryl sulfate complex*: injections are prepared by rapidly adding the required amount of water for injection, then further diluting with glucose 5% until the desired final concentration is reached.
- *amphotericin B-phospholipid complex*: before infusion the suspension concentrate must be diluted to the required final concentration with glucose 5%. The required amount of concentrate is injected via a sterile filter into the glucose 5%.

CAUTION: Mixture with sodium chloride injection 0.9% would precipitate amphotericin B.

Stability of oral suspensions. An oral suspension of amphotericin B 100 mg/mL, prepared from powder and a cherry-flavoured vehicle and maintained at pH 5.3, was found to be stable at 22 to 25° for 93 days.[1]

1. Dentinger PJ, *et al.* Stability of amphotericin B in an extemporaneously compounded oral suspension. *Am J Health-Syst Pharm* 2001; **58:** 1021–4.

Adverse Effects

Amphotericin B for intravenous use was originally only available in a conventional colloidal form; lipid formulations have been developed to reduce toxicity. The following adverse effects apply to the **conventional** form. Common adverse effects which occur during or after intravenous infusion of amphotericin B include headache, nausea, vomiting, chills, fever, malaise, muscle and joint pains, anorexia, diarrhoea, and gastrointestinal cramp. Hypertension, hypotension, cardiac arrhythmias including ventricular fibrillation and cardiac arrest, skin rashes, flushing, anaphylactoid reactions including bronchospasm and dyspnoea, blurred vision, tinnitus, hearing loss, vertigo, gastrointestinal bleeding, liver disorders, peripheral neuropathy, and convulsions have been reported occasionally.

Some degree of nephrotoxicity occurs in almost all patients given amphotericin B intravenously. Both tubular and glomerular damage occur; there may be improvement on cessation of therapy, but there is a risk of permanent renal impairment, particularly in patients given large cumulative doses (over 5 g). Renal tubular acidosis without systemic acidosis may develop. Use of amphotericin B is associated with increased urinary excretion of potassium and magnesium resulting in hypokalaemia and hypomagnesaemia respectively. Uric acid excretion is increased and nephrocalcinosis can occur. Limited data indicate that renal toxicity may be associated with sodium depletion; for strategies to improve sodium load see Nephrotoxicity, under Treatment of Adverse Effects, below.

A reversible, normocytic, normochromic anaemia develops in most patients given amphotericin B, possibly due to a direct suppressive effect on erythropoietin production. There are rare reports of thrombocytopenia, leucopenia, agranulocytosis, eosinophilia, and coagulation defects.

Leukoencephalopathy has been reported rarely in patients also receiving total body irradiation.

Amphotericin B solutions irritate the venous endothelium and may cause pain and thrombophlebitis at the injection site. Extravasation may cause tissue damage.

After intrathecal injection amphotericin B may also cause irritation of the meninges, neuropathy with pain, impaired vision, and retention of urine.

In general, adverse effects of **lipid** formulations have been similar to those of conventional amphotericin B, but are less frequent and less severe. Brief reversible episodes of renal impairment have been observed but these formulations have been considered to be safe enough to use in patients with renal impairment who