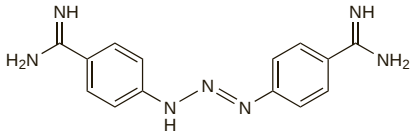
Diminazene Aceturate *(BANM, rINNM)*

Aceturato de diminazeno; Diminazène, Acéturate de; Diminazeni Aceturas. 1,3-Bis(4-amidinophenyl)triazene bis(*N*-acetylglycinate).

Диминазена Ацетурат

$C_{22}H_{29}N_9O_6$ = 515.5.

CAS — 536-71-0 (diminazene); 908-54-3 (diminazene aceturate).



(diminazene)

NOTE. Diminazene aceturate is often referred to by its veterinary proprietary name Berenil.

Profile

Diminazene aceturate, an aromatic diamidine derivative related to pentamidine, is an antiprotozoal that has been used in veterinary practice in the treatment of trypanosomiasis and babesiosis. It has also been tried in human infections.

Dinitolmide *(BAN, rINN)*

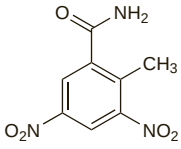
Dinitolmida; Dinitolmidum; Dinitrotoluamide; Methyldinitrobenzamide. 3,5-Dinitro-*o*-toluamide.

Динитолмид

$C_8H_7N_3O_5$ = 225.2.

CAS — 148-01-6.

ATC Vet — QP51AX12.



Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2008 (Dinitolmide). A cream to light tan powder. Practically insoluble in water; slightly soluble in alcohol, in chloroform, and in ether; soluble in acetone.

Profile

Dinitolmide is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry.

Eflornithine Hydrochloride

(BANM, USAN, rINNM)

DFMO; α-Difluoromethylornithine Hydrochloride; Éflornithine, Chlorhydrate d'; Eflornithini Hydrochloridum; Hidrocloruro de eflornitina; MDL-71782; MDL-71782A; RMI-71782. 2-(Difluoromethyl)-DL-ornithine monohydrochloride monohydrate.

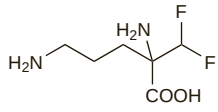
Эфлорнитина Гидрохлорид

$C_6H_{12}F_2N_2O_2$,HCl,H_2O = 236.6.

CAS — 67037-37-0 (eflornithine); 96020-91-6 (eflornithine hydrochloride).

ATC — D11AX16; P01CX03.

ATC Vet — QD11AX16.



(eflornithine)

Adverse Effects and Precautions

Myelosuppression may lead to anaemia, leucopenia, and thrombocytopenia. Some patients have had hearing loss and alopecia. Gastrointestinal disturbances, especially diarrhoea, may occur. Seizures have occurred in about 8% of patients given eflornithine but they may have been related to the disease rather than treatment.

Dosage should be reduced in patients with renal impairment.

Skin irritation, such as erythema or a stinging or burning sensation, has been reported after topical application of eflornithine.

Effects on the ears. A study in 58 patients[1] receiving eflornithine alone or with interferon alfa for the treatment of metastatic melanoma found that hearing loss was related to the cumulative dose of eflornithine and was worse in patients with pre-existing hearing deficit.

1. Croghan MK, *et al.* Dose-related α-difluoromethylornithine ototoxicity. *Am J Clin Oncol* 1991; **14:** 331–5.

Effects on the heart. Fatal cardiac arrest occurred in an AIDS patient with pneumocystis pneumonia during the intravenous infusion of eflornithine 100 mg/kg over 1 hour.[1] Sudden death after infusion of eflornithine had occurred in several other critically ill patients with AIDS.

1. Barbarash RA, *et al.* Alpha-difluoromethylornithine infusion and cardiac arrest. *Ann Intern Med* 1986; **105:** 141–2.

Pharmacokinetics

Eflornithine hydrochloride is absorbed from the gastrointestinal tract. After intravenous doses about 80% is excreted unchanged in the urine in 24 hours. The terminal elimination half-life is about 3 hours. It is distributed to the CSF.

Less than 1% of a dose is absorbed after topical application.

◊ References.

1. Haegele KD, *et al.* Kinetics of α-difluoromethylornithine: an irreversible inhibitor of ornithine decarboxylase. *Clin Pharmacol Ther* 1981; **30:** 210–17.
2. Milord F, *et al.* Eflornithine concentrations in serum and cerebrospinal fluid of 63 patients treated for Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1993; **87:** 473–7.
3. Malhotra B, *et al.* Percutaneous absorption and pharmacokinetics of eflornithine HCl 13.9% cream in women with unwanted facial hair. *J Clin Pharmacol* 2001; **41:** 972–8.

Uses and Administration

Eflornithine is an antiprotozoal that acts as an irreversible inhibitor of ornithine decarboxylase, the rate-limiting enzyme in polyamine biosynthesis; trypanosomes are more susceptible to the effects of eflornithine than are humans, probably because of their slower turnover of this enzyme.

Eflornithine is used in African trypanosomiasis due to *Trypanosoma brucei gambiense*. It is effective in the early and, more importantly, in the late stage of the disease (when there is CNS involvement).

In the treatment of African trypanosomiasis, eflornithine hydrochloride is given by intravenous infusion. The dose is 100 mg/kg every 6 hours for at least 14 days. Each dose should be given over a period of at least 45 minutes. Dosage should be reduced in patients with renal impairment.

Eflornithine hydrochloride is also applied topically twice daily for the reduction of unwanted facial hair in women. It is available as a cream containing 15% eflornithine hydrochloride monohydrate; in the UK this content is expressed as 11.5% eflornithine and in the USA as 13.9% anhydrous eflornithine hydrochloride.

Cryptosporidiosis. Eflornithine has been tried in the treatment of cryptosporidiosis (p.823) in AIDS patients.[1]

1. Rolston KVI, *et al.* Intestinal cryptosporidiosis treated with eflornithine: a prospective study among patients with AIDS. *J Acquir Immune Defic Syndr* 1989; **2:** 426–30.

Hirsutism. Topical eflornithine hydrochloride applied twice daily as a 13.9% cream is effective in reducing the growth of unwanted facial hair in females (see Hirsutism, p.2089), although it must be used indefinitely to prevent regrowth.[1] Its action is thought to be due to the irreversible inhibition of ornithine decarboxylase in hair follicles. It has also been used successfully in combination with laser hair removal.[2]

1. Barman Balfour JA, McClellan K. Topical eflornithine. *Am J Clin Dermatol* 2001; **2:** 197–201.
2. Hamzavi I, *et al.* A randomized bilateral vehicle-controlled study of eflornithine cream combined with laser treatment versus laser treatment alone for facial hirsutism in women. *J Am Acad Dermatol* 2007; **57:** 54–9.

Malignant neoplasms. Eflornithine has antimetabolic activity and is being studied as a potential chemopreventive agent in patients at high risk of a variety of malignant diseases, including cancer of the bladder, breast, cervix, colon, oesophagus, prostate, and skin.[1]

1. Meyskens FL, Gerner EW. Development of difluoromethylornithine (DFMO) as a chemoprevention agent. *Clin Cancer Res* 1999; **5:** 945–51.

African trypanosomiasis. Eflornithine is effective in the treatment of *Trypanosoma brucei gambiense* infections (p.827), and is particularly valuable in providing an alternative to melarsoprol in meningoencephalitic disease.[1-3] Eflornithine 100 mg/kg intravenously every 6 hours for 7 days, rather than the standard 14 days, produced long-term responses in 42 of 47 patients who had relapsed after other treatment regimens.[4] Similar positive results in relapsing cases were obtained with a short 7-day course in a multicentre randomised controlled study,[5] although this short course was inferior to the 14-day course for new cases, in whom it could not be recommended. A patient who had relapsed after treatment with melarsoprol and eflornithine given singly was cured when the drugs were given together.[6] Eflornithine is not effective when given alone in *T. b. rhodesiense* infections, and early reports of its use with suramin were not encouraging.[7] However, benefit has been reported from use with nifurtimox.[8]

1. Chappuis F, *et al.* Eflornithine is safer than melarsoprol for the treatment of second-stage *Trypanosoma brucei gambiense* human African trypanosomiasis. *Clin Infect Dis* 2005; **41:** 748–51.
2. Balasegaram M, *et al.* Melarsoprol versus eflornithine for treating late-stage Gambian trypanosomiasis in the Republic of the Congo. *Bull WHO* 2006; **84:** 783–91.
3. Priotto G, *et al.* Safety and effectiveness of first line eflornithine for *Trypanosoma brucei gambiense* sleeping sickness in Sudan: cohort study. *BMJ* 2008; **336:** 705–8.
4. Khonde N, *et al.* A seven days course of eflornithine for relapsing Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1997; **91:** 212–13.
5. Pepin J, *et al.* Short-course eflornithine in Gambian trypanosomiasis: a multicentre randomized controlled trial. *Bull WHO* 2000; **78:** 1284–95.
6. Simarro PP, Asumu PN. Gambian trypanosomiasis and synergism between melarsoprol and eflornithine: first case report. *Trans R Soc Trop Med Hyg* 1996; **90:** 315.
7. Clerinx J, *et al.* Treatment of late stage rhodesiense trypanosomiasis using suramin and eflornithine: report of six cases. *Trans R Soc Trop Med Hyg* 1998; **92:** 449–50.
8. Priotto G, *et al.* Nifurtimox-eflornithine combination therapy for second-stage *Trypanosoma brucei gambiense* sleeping sickness: a randomized clinical trial in Congo. *Clin Infect Dis* 2007; **45:** 1435–42.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Vaniqa; ***Cz.:*** Vaniqa; ***Fr.:*** Vaniqa; ***Ger.:*** Vaniqa; ***Irl.:*** Vaniqa; ***Ital.:*** Vaniqa; ***Neth.:*** Vaniqa; ***Port.:*** Vaniqa; ***Spain:*** Vaniqa; ***UK:*** Vaniqa; ***USA:*** Ornidyl; Vaniqa.

Emetine Hydrochloride *(BANM)*

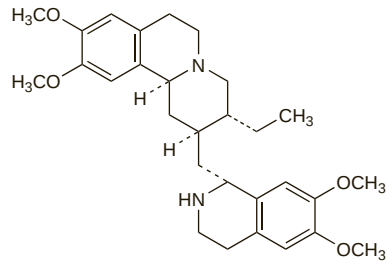
Cloridrato de Emetina; Emet. Hydrochlor.; Emetiinihydrokloridi; Emetina, hidrocloruro de; Emetin-dihydrochlorid; Émétine, chlorhydrate d'; Emetine Dihydrochloride; Emetin-hidroklorid; Emetinhydroklorid; Emetini Chloridum; Emetini Dihydrochloridum; Emetini hydrochloridum; Emetino hidrochloridas; Emetyny dichlorowodorek; Ipecine Hydrochloride; Methylcephaëline Hydrochloride. 6′,7′,10,11-Tetramethoxyemetan dihydrochloride heptahydrate; (2*S*,3*R*,11b*S*)-3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2-[(1*R*)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolylmethyl]-2*H*-benzo[*a*]quinolizine dihydrochloride heptahydrate.

Эметина Гидрохлорид

$C_{29}H_{40}N_2O_4$,2HCl,$7H_2O$ = 679.7.

CAS — 483-18-1 (emetine); 316-42-7 (anhydrous emetine hydrochloride); 7083-71-8 (emetine hydrochloride, hydrate); 79300-08-6 (emetine hydrochloride, heptahydrate).

ATC — P01AX02.



(emetine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Viet.*

Eur. also has a monograph for Emetine Hydrochloride Pentahydrate; *Int.* permits the heptahydrate or pentahydrate in the same monograph. *US* has a monograph for the anhydrous salt.

Ph. Eur. 6.2 (Emetine Hydrochloride Heptahydrate; Emetine Hydrochloride BP 2008). A white or slightly yellow crystalline powder. Freely soluble in water and in alcohol. A 2% solution in water has a pH of 4.0 to 6.0. Protect from light.

Ph. Eur. 6.2 (Emetine Hydrochloride Pentahydrate). A white or slightly yellow crystalline powder. Freely soluble in water and in alcohol. A 2% solution in water has a pH of 4.0 to 6.0. Protect from light.

USP 31 (Emetine Hydrochloride). The hydrochloride of an alkaloid obtained from ipecacuanha, or prepared by methylation of cephaëline, or prepared synthetically. Anhydrous emetine hydrochloride is a white or slightly yellowish, odourless, crystalline powder. Freely soluble in water and in alcohol. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects

Emetine hydrochloride is commonly associated with aching, tenderness, stiffness, and weakness of the muscles in the area of the injection site; there may be necrosis and abscess formation. After injection, diarrhoea and nausea and vomiting, sometimes with dizziness and headache, are common. There may be generalised muscle weakness and muscular pain, especially in the neck and limbs, and, more rarely, mild sensory disturbances. Eczematous, urticarial, and purpuric skin lesions have been reported.

Cardiovascular effects are considered the most serious and include precordial pain, dyspnoea, tachycardia, and hypotension. Changes in the ECG, particularly flattening or inversion of the T-wave and prolongation of the QT interval, occur in many patients. Emetine accumulates in the body and large doses or prolonged use may cause lesions of the heart, gastrointestinal tract, kidneys, liver, and skeletal muscle. Severe acute degenerative myocarditis may occur and may give rise to sudden cardiac failure and death. In some patients cardiotoxic effects have appeared after the completion of treatment with therapeutic doses.

Emetine hydrochloride is very irritant and contact with mucous membranes should be avoided.

Precautions

Emetine is contra-indicated in cardiac, renal, or neuromuscular disease. Its use should be avoided during pregnancy and it should not be given to children, except in severe amoebic dysentery unresponsive to other drugs. It should be used with great caution in old or debilitated patients. Patients given emetine should be closely supervised; ECG monitoring is advisable during treatment.

Pharmacokinetics

After injection emetine hydrochloride is concentrated in the liver, and to some extent in kidney, lung, and spleen. Excretion is slow and detectable amounts may persist in urine 40 to 60 days after treatment has been stopped.

Uses and Administration

Emetine, an alkaloid of ipecacuanha (p.1562), is a tissue amoebicide acting principally in the bowel wall and in the liver. It has been given by deep subcutaneous or intramuscular injection in the treatment of severe invasive amoebiasis (p.822), including hepatic amoebiasis in patients who do not respond to metronidazole, although dehydroemetine has tended to replace it. Emetine was formerly given orally as emetine and bismuth iodide.

Emetine has also been included in combination preparations for the symptomatic relief of cough.

Preparations

USP 31: Emetine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Spirbon; ***Cz.:*** Ipecarin†; Kodynal†; ***Hung.:*** Radipon; ***Switz.:*** Ipeca†; Sano Tuss.

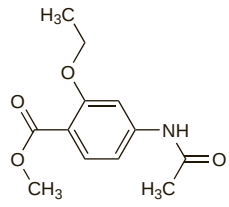
Ethopabate *(BAN)*

Etopabato. Methyl 4-acetamido-2-ethoxybenzoate.

$C_{12}H_{15}NO_4$ = 237.3.

CAS — 59-06-3.

ATC Vet — QP51AX17.



Pharmacopoeias. In *US* for veterinary use only. Also in *BP(Vet)*.

BP(Vet) 2008 (Ethopabate). A white or pinkish-white powder. Very slightly soluble in water; sparingly soluble in alcohol; soluble in chloroform and in methyl alcohol; slightly soluble in ether.

USP 31 (Ethopabate). A white or pinkish-white, odourless or practically odourless, powder. Very slightly soluble in water; soluble in dehydrated alcohol, in acetone, in methyl alcohol, and in acetonitrile; slightly soluble in ether; sparingly soluble in dichloromethane, in dioxan, in ethyl acetate, and in isopropyl alcohol. Protect from light.

Profile

Ethopabate is an antiprotozoal used in veterinary practice with other drugs, such as amprolium, for the control of coccidiosis in poultry.

Etofamide *(rINN)*

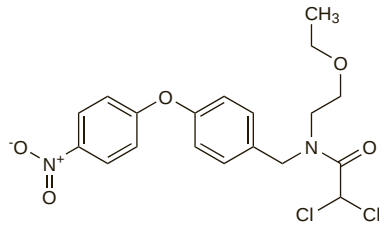
Ethychlordiphene; Etofamida; Étofamide; Etofamidum; K-430. 2,2-Dichloro-*N*-(2-ethoxyethyl)-*N*-[4-(4-nitrophenoxy)benzyl]-acetamide.

Этофамид

$C_{19}H_{20}Cl_2N_2O_5$ = 427.3.

CAS — 25287-60-9.

ATC — P01AC03.



Profile

Etofamide, a dichloroacetamide derivative, is a luminal amoebicide with actions and uses similar to those of diloxanide furoate (p.832).

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Kitnos; ***Mex.:*** Kitnos; ***Philipp.:*** Kitnos.

Fumagillin *(BAN, rINN)*

Fumagilina; Fumagilliini; Fumagilline; Fumagillinum. 4-(1,2-Epoxy-1,6-dimethylhex-4-enyl)-5-methoxy-1-oxaspiro[2.5]oct-6-yl hydrogen deca-2,4,6,8-tetraenedioate.

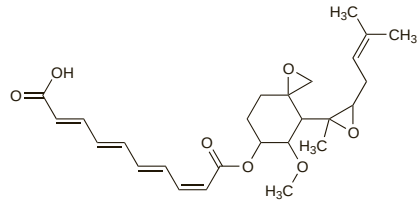
Фумагиллин

$C_{26}H_{34}O_7$ = 458.5.

CAS — 23110-15-8.

ATC — P01AX10.

ATC Vet — QP51AX23.



Profile

Fumagillin is an alicyclic antibiotic produced by certain strains of *Aspergillus fumigatus*. It has activity against Microsporidia and is used in veterinary practice to control *Nosema apis* infection in honeybees. Fumagillin is given in an oral dose of 20 mg three times daily for 14 days in the treatment of diarrhoea due to intestinal microsporidial infection with *Enterocytozoon bieneusi* in patients with HIV infection. It has also been tried in humans in the topical treatment of microsporidial keratoconjunctivitis. It was formerly given orally in the treatment of intestinal amoebiasis, but produced an unacceptably high frequency of adverse effects. Analogues of fumagillin have been studied for effects on angiogenesis in solid tumours.

Microsporidiosis. As discussed on p.826, topical treatment of microsporidial keratoconjunctivitis has been disappointing. There have been several reports of successful treatment in individual patients using fumagillin topically,[1-3] usually as a solution of bicyclohexylammonium fumagillin containing the equivalent of fumagillin 70 micrograms/mL.

Oral fumagillin has been effective in the treatment of diarrhoea due to intestinal microsporidial infection with *Enterocytozoon bieneusi* in patients with HIV infection.[4-7]

1. Rosberger DF, *et al.* Successful treatment of microsporidial keratoconjunctivitis with topical fumagillin in a patient with AIDS. *Cornea* 1993; **12:** 261–5.
2. Diesenhouse MC, *et al.* Treatment of microsporidial keratoconjunctivitis with topical fumagillin. *Am J Ophthalmol* 1993; **115:** 293–8.
3. Garvey MJ, *et al.* Topical fumagillin in the treatment of microsporidial keratoconjunctivitis in AIDS. *Ann Pharmacother* 1995; **29:** 872–4.
4. Molina J-M, *et al.* Potential efficacy of fumagillin in intestinal microsporidiosis due to Enterocytozoon bieneusi in patients with HIV infection: results of a drug screening study. *AIDS* 1997; **11:** 1603–10.
5. Molina J-M, *et al.* Trial of oral fumagillin for the treatment of intestinal microsporidiosis in patients with HIV infection. *AIDS* 2000; **14:** 1341–8.
6. Molina J-M, *et al.* Fumagillin treatment of intestinal microsporidiosis. *N Engl J Med* 2002; **346:** 1963–9.
7. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Flisint.

Furazolidone *(BAN, rINN)*

Furatsolidoni; Furazolidon; Furazolidona; Furazolidonum; Nifurazolidonum. 3-(5-Nitrofurfurylideneamino)-2-oxazolidone.

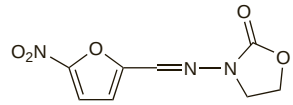
Фуразолидон

$C_8H_7N_3O_5$ = 225.2.

CAS — 67-45-8.

ATC — G01AX06.

ATC Vet — QG01AX06.



Pharmacopoeias. In *Br.*, *Fr.*, and *US*.

BP 2008 (Furazolidone). A yellow odourless or almost odourless crystalline powder. Very slightly soluble in water and in alcohol; slightly soluble in chloroform; practically insoluble in ether. The filtrate from a 1% suspension in water has a pH of 4.5 to 7.0. Protect from light.

USP 31 (Furazolidone). A yellow, odourless, crystalline powder. Practically insoluble in water, in alcohol, and in carbon tetrachloride. Store in airtight containers. Protect from light and avoid exposure to direct sunlight.

Adverse Effects

The most common adverse effects of furazolidone involve the gastrointestinal tract and include nausea and vomiting. Dizziness, drowsiness, headache, and a general malaise have also been reported.

Allergic reactions, most commonly skin reactions such as rashes or angioedema, may occur. There have been instances of acute pulmonary reactions, similar to those seen with the structurally related drug nitrofurantoin, and of hepatotoxicity. Agranulocytosis has been reported rarely. Haemolytic anaemia may occur in patients with G6PD deficiency given furazolidone.

Darkening of the urine has been attributed to the presence of metabolites.

Precautions

Furazolidone should be used with caution in those with G6PD deficiency because of the risk of haemolytic anaemia. It should not be given to infants under 1 month of age since their enzyme systems are immature.

Interactions

A disulfiram-like reaction has been reported in patients taking alcohol while on furazolidone therapy; alcohol should be avoided during, and for a short period after, treatment with furazolidone.

Furazolidone is an MAOI and the cautions advised for these drugs regarding use with other drugs, especially indirect-acting sympathomimetic amines, and the consumption of food and drink containing tyramine, should be observed (see Phenelzine Sulfate, p.417). However, there appear to be no reports of hypertensive crises in patients receiving furazolidone and it has been suggested that, since furazolidone inhibits monoamine oxidase gradually over several days, the risks are small if treatment is limited to a 5-day course. Toxic psychosis has been reported in a patient receiving furazolidone and amitriptyline (see Antiprotozoals, under Interactions of Amitriptyline, p.380).

Pharmacokinetics

Although furazolidone has been considered to be largely unabsorbed when given orally, the occurrence of systemic adverse effects and coloured metabolites in the urine suggest that this may not be the case. Rapid and extensive metabolism, possibly in the intestine, has been proposed.

Uses and Administration

Furazolidone is a nitrofuran derivative with antiprotozoal and antibacterial activity. It is active against the protozoan *Giardia intestinalis* (*Giardia lamblia*) and against a range of enteric bacteria *in vitro*, including staphylococci, enterococci, *Escherichia coli*, *Salmonella* spp., *Shigella* spp., and *Vibrio cholerae*. Furazolidone is bactericidal and appears to act by interfering with bacterial enzyme systems. Resistance is reported to be limited. It is used in the treatment of giardiasis (p.824) and cholera (p.172). It has been suggested for other bacterial gastrointestinal infections,