Profile
Closantel is an anthelmintic used in veterinary medicine for the treatment of fluke and nematode infections.

Effects on the eyes. Loss of eyesight was reported in 11 women who received closantel (Flukiver) in mistake for a gynaecological product.[1] Sight was restored after closantel was stopped but incapacitating eye pain remained.

1. 't Hoen E, *et al.* Harmful human use of donated veterinary drug. *Lancet* 1993; **342:** 308–9.

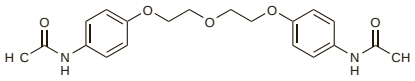
Diamfenetide *(BAN, rINN)*

Diamfenetida; Diamfénétide; Diamfenetidum; Diamphenethide. β,β′-Oxybis(aceto-*p*-phenetidide).

Диамфенетид

$C_{20}H_{24}N_2O_5$ = 372.4.

CAS — 3614 1-82-9.



Profile
Diamfenetide is an anthelmintic that has been used in veterinary medicine for the control of fascioliasis in sheep.

Dichlorophen *(BAN, rINN)*

Dichlorophène; Dichlorophenum; Diclorofeno; Di-phenthane-70; G-4. 2,2′-Methylenebis(4-chlorophenol).

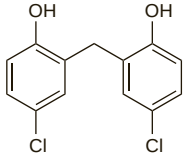
Дихлорофен

$C_{13}H_{10}Cl_2O_2$ = 269.1.

CAS — 97-23-4.

ATC — P02DX02.

ATC Vet — QP52AG01.



Pharmacopoeias. In *Br.* and *Fr.*

BP 2008 (Dichlorophen). A white or slightly cream-coloured powder with a not more than slightly phenolic odour. Practically insoluble in water; freely soluble in alcohol; very soluble in ether.

Profile
Dichlorophen is an anthelmintic that was used in the treatment of infection by tapeworms but has been superseded by praziquantel or niclosamide.

Dichlorophen also has antifungal and antibacterial activity and has been used topically in the treatment of fungal infections and as a germicide in soaps and cosmetics.

Preparations
BP 2008: Dichlorophen Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***S.Afr.:*** Mycota†; ***UK:*** Mycota.

Diethylcarbamazine Citrate

(BANM, rINNM)

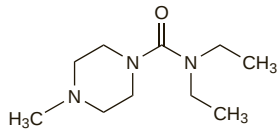
Citrato de dietilcarbamazina; Diethylcarbam. Cit.; Diethylcarbamazine Acid Citrate; Diéthylcarbamazine, citrate de; Diethylcarbamazini citras; Diethylkarbamazin-citrát; Dietilkarbamazin-citrát; Dietilkarbamazino citratas; Dietylkarbamazincitrat; Dietyylikarbamatsiinisitraatti; Ditrazini Citras; RP-3799. *NN*-Diethyl-4-methylpiperazine-1-carboxamide dihydrogen citrate.

Диэтилкарбамазина Цитрат

$C_{10}H_{21}N_3O,C_6H_8O_7$ = 391.4.

CAS — 90-89-1 (diethylcarbamazine); 1642-54-2 (diethylcarbamazine citrate).

ATC — P02CB02.



(diethylcarbamazine)

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

Ph. Eur. 6.2 (Diethylcarbamazine Citrate). A white or almost white, crystalline, slightly hygroscopic powder. Very soluble in water; soluble in alcohol; practically insoluble in acetone. Store in airtight containers.

USP 31 (Diethylcarbamazine Citrate). A white, crystalline, slightly hygroscopic powder, odourless or has a slight odour. Very soluble in water; sparingly soluble in alcohol; practically insoluble in acetone, in chloroform, and in ether. Store in airtight containers.

Adverse Effects
Adverse effects directly attributable to diethylcarbamazine include nausea and vomiting. Headache, dizziness, and drowsiness may occur.

Hypersensitivity reactions arise from the death of the microfilariae. These can be serious, especially in onchocerciasis where there may also be sight-threatening ocular toxicity; fatalities have been reported. Encephalitis may be exacerbated in patients with loiasis and fatalities have occurred.

◊ Reactions occurring during diethylcarbamazine treatment of **lymphatic filariasis** are basically of 2 types: pharmacological dose-dependent responses and a response of the infected host to the destruction and death of parasites.[1]

- Reactions of the first type include weakness, dizziness, lethargy, anorexia, and nausea. They begin within 1 to 2 hours of taking diethylcarbamazine, and persist for a few hours.
- Reactions of the second type are less likely to occur and are less severe in bancroftian than in brugian filariasis. They may be systemic or local, both with or without fever.

  Systemic reactions may occur a few hours after the first oral dose of diethylcarbamazine and generally do not last for more than 3 days. They include headache, aches in other parts of the body, joint pain, dizziness, anorexia, malaise, transient haematuria, allergic reactions, vomiting, and sometimes attacks of bronchial asthma in asthmatic patients. Fever and systemic reactions are positively associated with microfilaraemia. Systemic reactions are reduced if diethylcarbamazine is given in spaced doses or in repeated small doses. They eventually cease spontaneously and interruption of treatment is rarely necessary; symptomatic treatment with antipyretics or analgesics may be helpful.

  Local reactions tend to occur later in the course of treatment and last longer; they also disappear spontaneously and interruption of treatment is not necessary. Local reactions include lymphadenitis, abscess, ulceration, and transient lymphoedema; funiculitis and epididymitis may also occur in bancroftian filariasis.

It has been suggested that the release of interleukin-6 may be implicated in diethylcarbamazine's adverse effects in patients with lymphatic filariasis.[2]

In most patients with **onchocerciasis**, the microfilaricidal activity of diethylcarbamazine leads to a series of events with dermal, ocular, and systemic components, known as the *Mazzotti reaction*, within minutes to hours after its use.[3]

- Clinical manifestations can be severe, dangerous, and debilitating. Systemic reactions include increased itching, rash, headache, aching muscles, joint pain, painful swollen and tender lymph nodes, fever, tachycardia and hypotension, and vertigo. Most patients have eye discomfort in the first few hours after diethylcarbamazine treatment. Punctate keratitis can develop as can optic neuritis and visual field loss.

WHO no longer recommends the use of diethylcarbamazine in onchocerciasis as safer alternatives exist.

1. WHO. Lymphatic filariasis: the disease and its control: fifth report of the WHO expert committee on filariasis. *WHO Tech Rep Ser 821* 1992.
2. Yazdanbakhsh M, *et al.* Serum interleukin-6 levels and adverse reactions to diethylcarbamazine in lymphatic filariasis. *J Infect Dis* 1992; **166:** 453–4.
3. WHO. WHO expert committee on onchocerciasis: third report. *WHO Tech Rep Ser 752* 1987.

Precautions
Treatment with diethylcarbamazine should be closely supervised since hypersensitivity reactions are common and may be severe, especially in patients with onchocerciasis or loiasis. Patients with onchocerciasis should be monitored for eye changes. (The use of diethylcarbamazine to treat onchocerciasis is no longer recommended.) In patients with heavy *Loa loa* infection there is a small risk of encephalopathy and diethylcarbamazine should be stopped at the first sign of cerebral involvement.

Infants, pregnant women, the elderly, and the debilitated, especially those with cardiac or renal disease, are normally excluded when diethylcarbamazine is used in mass treatment schedules.

Pregnancy. Pregnant women are normally excluded when diethylcarbamazine is used in mass treatment schedules.

Animal studies[1] suggest that the uterine hypermotility induced by diethylcarbamazine is mediated via prostaglandin synthesis; this might explain the mechanism of the abortifacient action previously reported.[2]

1. Joseph CA, Dixon PAF. Possible prostaglandin-mediated effect of diethylcarbamazine on rat uterine contractility. *J Pharm Pharmacol* 1984; **36:** 281–2.
2. Subbu VSV, Biswas AR. Ecbolic effect of diethyl carbamazine. *Indian J Med Res* 1971; **59:** 646–7.

Renal impairment. For a study on the effects of renal impairment on the pharmacokinetics of diethylcarbamazine, see under Pharmacokinetics, below.

Pharmacokinetics
Diethylcarbamazine is readily absorbed from the gastrointestinal tract and also through the skin and conjunctiva. It is widely distributed in tissues and is mainly excreted in the urine unchanged and as the *N*-oxide metabolite. Urinary excretion and hence plasma half-life is dependent on urinary pH. About 5% of a dose is eliminated in the faeces.

Disposition. A pharmacokinetic study in 6 patients with onchocerciasis[1] indicated that diethylcarbamazine is absorbed quickly and almost completely from the gastrointestinal tract, and is eliminated largely as unchanged drug in urine, with relatively small amounts being excreted as the *N*-oxide metabolite. After a single radioactively labelled oral dose of diethylcarbamazine citrate 0.5 mg/kg given as an aqueous solution, peak plasma concentrations of 100 to 150 nanograms/mL were achieved in 1 to 2 hours, followed by a sharp decline, then a marked secondary rise 3 to 6 hours after dosing, followed by a steady decline. The half-life ranged from 9 to 13 hours. Urinary excretion of diethylcarbamazine and diethylcarbamazine *N*-oxide was complete within 96 hours; between 4 and 5% of the dose was recovered in the faeces. Disposition was similar in 5 healthy subjects given a single 50-mg tablet of diethylcarbamazine citrate. Peak plasma concentrations were initially 80 to 200 nanograms/mL, with a secondary rise 3 to 9 hours after dosing, the terminal half-life ranged from 5 to 13 hours, and urinary excretion of unchanged diethylcarbamazine and the *N*-oxide was complete within 48 hours.

When an alkaline urinary pH was maintained, the elimination half-life of diethylcarbamazine and the area under the plasma concentration versus time curve were significantly increased compared with when an acidic urinary pH was maintained.[2]

1. Edwards G, *et al.* Diethylcarbamazine disposition in patients with onchocerciasis. *Clin Pharmacol Ther* 1981; **30:** 551–7.
2. Edwards G, *et al.* The effect of variations in urinary pH on the pharmacokinetics of diethylcarbamazine. *Br J Clin Pharmacol* 1981; **12:** 807–12.

Renal impairment. Results in patients with chronic renal impairment and in healthy subjects, given a single 50-mg oral dose of diethylcarbamazine citrate, indicated that the plasma half-life of diethylcarbamazine is prolonged and its 24-hour urinary excretion considerably reduced in those with moderate and severe degrees of renal impairment.[1] Mean plasma half-lives in 7 patients with severe renal impairment (creatinine clearance less than 25 mL/minute), in 5 patients with moderate renal impairment (creatinine clearance between 25 and 60 mL/minute), and in 4 healthy subjects, were 15.1, 7.7, and 2.7 hours, respectively. The patient with the longest plasma half-life of 32 hours did not have the poorest renal function, but it was considered likely that the abnormally slow elimination of diethylcarbamazine was due to the high urinary pH (7) resulting from sodium bicarbonate therapy. A further patient with a half-life longer than expected also had a less acidic urine.

1. Adjepon-Yamoah KK, *et al.* The effect of renal disease on the pharmacokinetics of diethylcarbamazine in man. *Br J Clin Pharmacol* 1982; **13:** 829–34.

Uses and Administration
Diethylcarbamazine is an anthelmintic used in the treatment of lymphatic filariasis due to *Wuchereria bancrofti* (bancroftian filariasis), *Brugia malayi*, or *B. timori* (both known as brugian filariasis and as Malayan and Timorian filariasis respectively). It is also used in loiasis due to *Loa loa*. It was used in onchocerciasis due to *Onchocerca volvulus* before ivermectin became available. Diethylcarbamazine is active against both the microfilariae and adult worms of *W. bancrofti*, *B. malayi*, and *Loa loa*, but only against the microfilariae of *O. volvulus*. It has been tried in *Mansonella* infections and may be most effective against *M. streptocer-*