



**National Agency for Food & Drug Administration &
Control (NAFDAC)**

**Registration & Regulatory Affairs (R & R)
Directorate**

**SUMMARY OF PRODUCT CHARACTERISTICS
(SmPC) TEMPLATE**

1. NAME OF THE MEDICINAL PRODUCT

Cenocide Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg Diethylcarbamazine citrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

The tablets are round, off white biconvex, branded and scored tablet coded A3A and inscribed SKG.

4. Clinical particulars

4.1 Therapeutic indications

Cenocide is indicated for:

- Lymphatic filarial infections due to *Wuchereria bancrofti* (bancroftian filariasis), *Brugia malayi* (malayan filariasis), and *Brugia timori* (timorian filariasis).
- Treatment of loiasis due to *Loa loa*
- Treatment of toxocariasis (visceral larval migrans).
- For the prophylaxis against loiasis

Method of administration

For oral use.

Posology

Diethylcarbamazine should be administered after meals.

Adults

Allergic manifestations induced by the action of diethylcarbamazine on the parasite are most commonly seen early in treatment. For this reason, the administration of diethylcarbamazine should commence with a low dose which is increased over the next 2 to 3 days and maintained for the remainder of the treatment period.

Treatment of lymphatic filariasis

The starting dose is 1 mg/kg on the first day. This dose is gradually increased over 2 to 3 days to 6 mg/kg daily, administered preferably in divided doses, for 12 to 14 days. The treatment may be repeated, if necessary, after a minimum delay of 10 days.

Treatment of tropical eosinophilia

The recommended dosage is 6 mg/kg daily for 14-21 days, repeated as necessary if symptoms reoccur.

Treatment of toxocariasis

The starting dose is 1 mg/kg twice daily. This dosage is gradually increased to 6 mg/kg daily, administered in two divided doses, for 21 days.

Treatment of Loiasis

In the case of severe microfilaraemia, treatment should be initiated under close medical supervision (see Special Warnings and Special Precautions for Use). Treatment should start with very small doses, increasing gradually over 3 days to 6–9 mg/kg daily, administered in three divided doses, for 21 days.

In order to mitigate or prevent the occurrence of side effects, diethylcarbamazine may be combined with corticosteroids.

Prophylaxis against Loiasis

The recommended dose is 300 mg once a week.

Children

In children, diethylcarbamazine should always be administered under close medical supervision and in divided daily doses.

Diethylcarbamazine citrate may be given orally to children for the treatment of lymphatic filariasis, loiasis and toxocariasis.

Treatment of lymphatic filariasis

For the treatment of lymphatic filariasis in children under 10 years of age should be given half the usual adult dose.

Treatment of Loiasis

For the treatment of loiasis children may be given a dose of 6 - 9 mg/kg daily in 3 divided doses for 12 days. Treatment should start with very small doses, increasing gradually over 3 days.

Treatment of toxocariasis

For the treatment of toxocariasis children may be given the same dose as for adults.

Elderly

There is no information on the effect of diethylcarbamazine on elderly individuals. The same pattern of adverse reactions associated with the use of diethylcarbamazine in the treatment of filarial infections should be expected. Therefore, older patients should be treated with careful attention to the normal precautions (see Section Special Warnings and Special Precautions for Use).

Renal Impairment

In patients with renal insufficiency urinary excretion of diethylcarbamazine is reduced and plasma half-life prolonged according to the degree of renal impairment. Therefore, doses need to be adjusted in these patients.

Hepatic Impairment

Dose reduction is not necessary.

4.2 Contraindications

This medicinal product is contraindicated in:

- Hypersensitivity to diethylcarbamazine citrate or to any of the excipients,
- Infants, pregnant women, the elderly and the debilitated, especially those with cardiac or renal disease. These group of persons are usually excluded when diethylcarbamazine is used in mass treatment schedules.
- The use of diethylcarbamazine to treat onchocerciasis is no longer recommended due to risk of severe hypersensitivity reactions in patients with onchocerciasis. If it is used, treatment should be closely monitored and patients should be monitored for eye changes.

4.3 Special warnings and precautions for use

Initial Treatment

During the first few days of treatment of filarial infections with diethylcarbamazine, patients should be monitored carefully for adverse reactions (see Section Undesirable Effects). The intensity and the severity of the adverse reactions that appear after administration of diethylcarbamazine citrate are associated with the level of microfilariae in the blood prior to treatment. In the event of Loa loa infestation, the level of microfilariae present in the blood is often high, which predisposes the treated patients to an increased risk of serious side effects (see Section Undesirable Effects).

The dosage should be increased gradually in individuals showing no or mild reactions and should be slower in individuals showing more severe reactions. In the large majority of cases, reactions resolve during treatment.

Serious central nervous system complications in patients with Loa loa infestation

Serious central nervous system problems such as encephalopathy and coma have been reported, in particular in patients with Loa loa infestation that have been treated with diethylcarbamazine. Although rare, fatalities have been reported.

These reactions can be mitigated or prevented by the introduction of a progressive dosage and the addition of corticosteroids.

Alkaline urine

Diets that promote the alkalinisation of the urine may increase the elimination half-life of diethylcarbamazine. Dose reductions may be needed.

Hypersensitivity Reactions

In the event of a severe hypersensitivity reaction, administration of a corticosteroid, such as betamethasone, is recommended.

Seizure threshold

Diethylcarbamazine must be used with care in patients who have a history of convulsions or factors that predispose them to convulsions.

Concomitant disorders

In the event of an acute concomitant disorder, the patient should be allowed to recover before taking diethylcarbamazine.

4.4 Interaction with other medicinal products and other forms of interaction

There are no relevant data available.

4.5 Pregnancy and Lactation

Fertility

There are no relevant data available.

Pregnancy

Diethylcarbamazine should not be used during pregnancy. In view of the severe reactions which may follow diethylcarbamazine administration, it is advisable to postpone treatment of pregnant women until after parturition.

Lactation

The use of diethylcarbamazine is not recommended during breast-feeding. No data are available on the excretion of diethylcarbamazine citrate or its metabolites in human breast milk

4.7 Effects on ability to drive and use machines

Patients should be informed of the risk of drowsiness associated with the use of diethylcarbamazine which may impact on the ability to drive and use machines (see Section Undesirable Effects).

4.8 Undesirable effects

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:

Very common $\geq 1/10$ <1/10

Common $\geq 1/100$ to <1/10

Rare $\geq 1/10000$ to <1/1000

Very rare <1/10000

Not known (cannot be estimated from the available data).

In the absence of a filarial infection the only side effects of diethylcarbamazine, when given at the recommended dosage, are nausea and vomiting.

Adverse reactions to treatment with diethylcarbamazine vary with the infecting filarial species. Treatment of bancroftian filariasis with diethylcarbamazine results in the development of fewer and milder reactions than those seen following therapy of infection with *Brugia* spp or *Loa loa*. Reactions associated with the microfilaricidal action of diethylcarbamazine resolve during treatment.

Blood and lymphatic system disorders

Not known: lymphadenitis^{1,2}, lymphangitis^{1,2}, lymphoedema^{1,2}

Immune system disorders

Not known: reactions resembling the Mazzotti reaction, allergic reactions (see Skin and subcutaneous tissue disorders)

Metabolism and nutrition disorders

Not known: anorexia

Nervous system disorders

Not known: dizziness, headache, seizures (in patients with history of epilepsy), meningoencephalitis³ (see Section Special Warnings and Special Precautions for Use)

Vascular disorders

Not known: inflammation around the vessels^{1,2}

Respiratory, thoracic and mediastinal disorders

Not known: asthmatic attack

Gastrointestinal disorders

Not known: nausea, vomiting

Skin and subcutaneous tissue disorders

Not known: urticaria, pruritus³, rash³

Musculoskeletal and connective tissue disorders

Not known: myalgia¹, arthralgia^{1,3}

Renal and urinary disorders

Not known: haematuria, proteinuria

General disorders and administration site conditions

Not known: fever, rigors, malaise, chills^{1,2}, localised oedema^{1,2}, oedema³, nodules^{1,2} (palpable subcutaneously and along spermatic cord, formed by recently killed worms)

¹ – in patients with *Brugia malayi* or *Brugia timori* infection

² – in patients with *Wuchereria bancrofti* infection

³ – in patients with *Loa loa* infection

4.9 Overdose

Symptoms and signs

Symptoms are likely to consist of nausea, vomiting, headache, dizziness, drowsiness and, in serious cases, convulsions.

Treatment

Adequate fluids should be given to ensure optimal diuresis. Acidification of urine should enhance the excretion of diethylcarbamazine. Routine supportive measures should be given when necessary.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antinematodal agents; ATC Code: P02CB02.

Mechanism of Action

The mode of action is uncertain. At least 2 types of effects of diethylcarbamazine on microfilariae have been reported. The drug has been shown to induce immobilization of the worm by decreasing muscle activity; this may be related to hyperpolarization effects caused by the piperazine moiety. Alteration of the surface membrane of microfilariae also appears to occur, facilitating enhanced destruction by the host's immune system. Recent evidence suggests that diethylcarbamazine may enhance adhesion of granulocytes to microfilariae via antibody-dependent and independent mechanisms. Platelets may also play a role in mediating effects against microfilariae. Interference of microfilarial intracellular processing and transport of specific macromolecules by diethylcarbamazine, or other effects of the drug on immune and/or inflammatory responses of the host have also been suggested to explain filaricidal actions.

Diethylcarbamazine is microfilaricidal for all species for which it is indicated. In addition, diethylcarbamazine leads to almost complete destruction of adult *Loa loa*; however it has variable macrofilaricidal activity against other filarial species.

5.2 Pharmacokinetic properties

Absorption

Diethylcarbamazine is rapidly absorbed from the gastrointestinal tract. After a single dose, peak plasma levels are reached within 1 to 2 hours. The plasma half life is approximately 9 hours. Increasing doses, given over several days, result in a proportional rise in plasma levels. When a daily maintenance dosage of 900 mg is given, the mean plasma level remains constant, showing no accumulation on prolonged dosing.

Distribution

Diethylcarbamazine is widely distributed in tissues. In animals, diethylcarbamazine distributes in similar amounts to most tissues, except adipose tissue. High drug concentrations have been found in the pituitary gland, lymph nodes, adrenal medulla, and salivary glands. Diethylcarbamazine crosses the blood-brain barrier.

Metabolism

Diethylcarbamazine is eliminated largely as unchanged drug, with relatively small amounts being excreted as the N-oxide metabolite. Elimination Diethylcarbamazine and its metabolites are excreted in the urine. Urinary excretion and hence plasma half-life is dependent on urinary pH. About 5% of a dose is eliminated in the faeces.

Special patient populations

Renal Impairment

The plasma half-life of diethylcarbamazine is increased in patients with renal insufficiency, whereas acidification of urine significantly increases the excretion rate of diethylcarbamazine, thereby markedly reducing the plasma half life.

Vegetarians

In certain regions, the diet is predominantly vegetarian, which promotes alkaline urine (pH 7.5 to 8). When an alkaline urinary pH is maintained, the elimination half-life of diethylcarbamazine is increased, whereas acidification of urine significantly increases the excretion rate of diethylcarbamazine.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis

There are no data as to whether diethylcarbamazine has mutagenic or carcinogenic potential.

Teratogenicity

Diethylcarbamazazine is not teratogenic at high doses in rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize Starch
Gelatin
Acacia Powder
Magnesium Stearate
Calcium Silicate

6.2 Incompatibilities

There are no relevant data available.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store above 30°C. Keep Dry.
Keep out of the reach of children.

6.5 Nature and contents of container

The tablets are packed in HDPE tins with pilfer proof caps.
The securitainers are then packed into a carton box.
Packs containing 100 and 1000 tablets.

6.6 Special precautions for disposal

There are no special requirements for use or handling of this product.

7 APPLICANT/MANUFACTURER

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