DIETHYL-50
(Vardhman Exports),

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DIETHYLCARBAMAZINE CITRATE TABLETS BP 50mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Diethylcarbamazine Citrate BP 50mg

Excipients with known effects:

Each tablet contains 50.00 mg of Lactose, 2.5 mg of Magnesium Stearate.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

White circular, flat, uncoated tablets having embossing “DIETHYL” on one side and breakline on other side of each tablet.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diethylcarbamazine Citrate Tablets, in combination with Albendazole, are indicated in adults and in children over 2 years for large scale preventative chemotherapy interventions for the control of lymphatic filariasis, following the recommendations of the WHO Global Programme to Eliminate Lymphatic Filariasis.

The mass drug administration (MDA) programme consists of administering a single annual dose of Diethylcarbamazine citrate 6 mg/kg with Albendazole 400 mg to affected communities, in areas where onchocerciasis is not co-endemic (see section 4.3).

4.2 Posology and method of administration

Posology

Diethylcarbamazine Citrate Tablets should be co-administered with a single dose of Albendazole 400 mg tablets.

Adults
The usual dose is 6 mg per kg of body weight Diethylcarbamazine citrate given as a single dose administered once per year for 4 to 6 years.

Children
In children over 2 years, the usual dose is 6 mg per kg of body weight Diethylcarbamazine citrate given as a single dose administered once per year for 4 to 6 years.

Method of administration

For Oral use.

The tablets should be swallowed and not chewed. Diethylcarbamazine Citrate Tablets should preferably be administered after meals.

4.3 Contraindications

Co-infection with onchocerciasis. Serious ocular damage may occur.

4.4 Special warnings and precautions for use

Use of Diethylcarbamazine citrate in patients without underlying filarial infestation
Diethylcarbamazine citrate must be used with care in patients who have a history of convulsions or who show factors that predispose them to convulsions (see section 4.8).

Severely ill persons
The frail, elderly and debilitated, especially those with cardiac or renal disease, are normally excluded when Diethylcarbamazine citrate is used in MDA programmes. In the event of a concomitant disorder, the patient should be allowed to recover before taking Diethylcarbamazine citrate.
Diethylcarbamazine Citrate Tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance.

Children
Children under the age of 2 years are normally excluded when Diethylcarbamazine citrate is used in MDA programmes.
Use of Diethylcarbamazine citrate in patients with underlying filarial infestation

Lymphatic filariasis
Patients with symptoms suggesting lymphatic filariasis (swelling of legs, arms, female breast or male genitalia) should be managed according to the relevant local or international treatment guidelines. For WHO options for treatment, see references at end of this SmPC, under Section 4.2

Loa loa
The intensity and the severity of the undesirable effects 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 very high, which predisposes the treated patients to an increased risk of serious side effects. Serious central nervous system problems such as encephalopathy and coma have been observed in patients with *Loa loa* infections that have been treated with Diethylcarbamazine citrate, in particular.

Onchocerciasis
Diethylcarbamazine must not be administered in patients co-infected with onchocerciasis. Skin and/or systemic reactions of variable severity (Mazzotti reaction) and eye reactions have been observed after administration of drugs with rapid microfilariacidal action such as Diethylcarbamazine citrate. If there is evidence of hypersensitivity to the eye, administration must be stopped due to potential sight loss. These manifestations are probably associated with an inflammatory process that is triggered following the death of microfilariae and the release of decomposition products.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of Diethylcarbamazine citrate with Albendazole did not significantly alter the PK profile of either drug. Adequate absorption of both Diethylcarbamazine and Albendazole was observed in both adults and children aged over 5 years.
No other known interactions.

4.6. Fertility, Pregnancy and lactation

Pregnancy
The potential risk to the fetus in humans is unknown.
Diethylcarbamazine Citrate Tablets should not be used in pregnancy, and as such, pregnant women are normally excluded when Diethylcarbamazine citrate is used in MDA.

Breastfeeding
It is unknown whether Diethylcarbamazine or its metabolites are excreted in human milk. As a risk to the newborn or infant cannot be excluded, the product should not be given to breastfeeding women.

Fertility
The potential risk for humans is unknown. No specific studies with Diethylcarbamazine citrate in humans have been conducted to evaluate effects on fertility.

4.7 Effects on ability to drive and use machines

Diethylcarbamazine Citrate Tablets may cause short term drowsiness which may impact on the ability to drive and use machines (see section 4.8). Vehicle drivers and machine users should be informed of the risk of drowsiness related to using this medicinal product.

4.8 Undesirable effects

Diethylcarbamazine Citrate Tablets should Only Be Used As Part Of A Mass Drug Administration Programme For Elimination Of Lymphatic Filariasisin Areas Where Onchocerciasis Is Not Co-Endemic. Use As Directed.

There is no clear information on the frequency of adverse reactions occurring as a result of Diethylcarbamazine citrate administration. Mild to moderate adverse reactions are common,but the incidence of serious adverse reactions is considered to be very low.

In the absence of circulating microfilaraemia, the administration of Diethylcarbamazine citrate, when given at the recommended dosage, may cause nausea, vomiting, abdominal pain, diarrhoea, loss of appetite, muscle pain, dizziness, drowsiness, fatigue and headache. These begin within one to two hours and may persist for several hours.

In patients with circulating microfilaraemia adverse reactions may be more common and severe, particularly in patients with a high parasite burden. Adverse reactions vary with the infecting filarial species, may be local and/or systemic, and may occur with or without fever. These are considered allergic reactions due to antigen-antibody reaction caused by dead microfilariae or adult filarial worms, and the intensity and the severity of adverse reactions are usually associated with the level of microfilariae in the blood prior to treatment. Usually such symptoms are transient and self-limiting, but when the symptoms are significant enough to interfere with daily life, the patient needs to be observed carefully and given clinically appropriate treatment. Steroids have been used. If there is evidence of hypersensitivity involving the eye, administration must be stopped due to potential sight loss (see section 4.4).

System Organ Class	**Reactions attributable to DEC (may be seen in subjects without microfilariae)**	**Reactions attributable to death of microfilariae (may be seen in subjects with microfilariae and/or adult worm infections)**
Blood and lymphatic system disorders	Lymphadenitis, lymphangitis, lymph node abscess, lymph node pain, lymphoedema	
Gastrointestinal disorders	Nausea, vomiting, abdominal pain, diarrhoea	Abdominal pain, nausea, vomiting, diarrhoea
General disorders and administration site conditions	Pyrexia, chills, weakness, malaise	
Metabolism and nutrition disorders	Decreased appetite	Decreased appetite
Musculoskeletal and connective tissue disorders	Myalgia	Myalgia, arthralgia, chest pain

Nervous system disorders	Dizziness, somnolence, lethargy, headache	Dizziness, headache, lethargy
Renal and urinary disorders	Haematuria	
Reproductive system and breast disorders	Epididymitis, spermatic cord inflammation, hydrocele, scrotal mass	
Respiratory disorders	Dyspnoea, cough	
Skin and subcutaneous tissue disorders	Pruritus, papular rash	
Vascular disorders	Circulatory collapse, orthostatic hypotension	
Reactions only observed in subjects with loaisis or onchocerciasis infection (see section 4.3)		
Cardiac disorders	Tachycardia	
Eye disorders	Optic neuritis, punctate keratitis, iridocyclitis, conjunctivitis, visual field defect, eye pain, lacrimation, photophobia, corneal oedema	
Immune system disorders	Mazotti reaction	
Infections and infestations	Meningoencephalitis helminthic	
Investigations	Increased intraocular pressure	
Nervous system disorders	Coma, allergic encephalitis, encephalopathy, vertigo, convulsion (isolated cases in patients with a history of epilepsy)	
Renal and urinary disorders	Proteinuria	
NOTE: frequency of all reactions is unknown (cannot be estimated from the available data). DEC = diethylcarbamazine citrate.		

Children
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Symptoms
Overdose may cause nausea, vomiting, headache, vertigo, drowsiness and, in rare but serious cases, convulsions.

Management
Administration of activated charcoal may be of value. Monitor for adverse reactions, with symptomatic treatment and hospitalisation if necessary.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antihelmintics,
ATC code: P02CB02

Mechanism of action
Diethylcarbamazine citrate is a synthetic piperazine derivative with an antihelmintic action.
MDA of diethylcarbamazine citrate has potential to interrupt the parasitic life cycle by destruction of microfilariae which are essential for host to vector transmission of the parasite. The basic principle of MDA is to suppress microfilaraemia to levels at which transmission is not possible.

The mode of action of diethylcarbamazine citrate is not clearly known. Diethylcarbamazine citrate can be best described as a potent anti-microfilaraemic agent with variable macrofilaricidal properties. The drug is known to exert its effect directly on the parasite and also achieve parasite killing by activating the host immune response. Several potential modes of action of diethylcarbamazine citrate leading to microfilariae killing have been identified:

- Overstimulation of the neuromuscular system of the parasites and increased motility, inhibition of vital parasite metabolic enzymes, activation of surface membrane complement, activation of eosinophils and release of eosinophil-derived cationic proteins, enhanced eosinophil-dependent antibody mediated destruction of parasites and increased adhesion of parasites to phagocytic and antibody producing cells.
- Inhibition of acetylcholinesterase production by parasites, leading to increased levels of lysosomal enzymes β-glucuronidase and acid phosphatase that are involved in phagocytosis.
- Release of nitric oxide as evidenced by increased levels of nitrite and nitrates.
- Changes in arachidonic acid metabolism in the parasite and the host that alter adhesiveness of the parasite.

The mode of action of diethylcarbamazine citrate on adult worms is less well documented. However, there is sufficient evidence to suggest that diethylcarbamazine is macrofilaricidal. Degenerating adult worms have been demonstrated in lymph nodes post-treatment. It is also well known that the macrofilaricidal effects are inconsistent.

Diethylcarbamazine citrate was found to have effects on the arachidonic acid and cyclooxygenase metabolic pathways and COX-1 pathway of filaria. It has also been determined that inducible nitric oxide is essential for the rapid sequestration of microfilariae by diethylcarbamazine citrate. It has been suggested that as diethylcarbamazine citrate alters arachidonic acid metabolism in microfilariae (and in host endothelial cells), these changes may result in vasoconstriction and amplified endothelial adhesion, leading to immobilization of microfilarial parasites, enhanced adherence, and cytotoxic activity by host platelets and granulocytes. This would represent activation of the innate, nonspecific immune system, independent of the adaptive, antigen-specific, immune response.

Pharmacodynamic effects

Decrease of microfilariae in blood

Administration of diethylcarbamazine citrate (6 mg/kg) and albendazole 400 mg resulted in a decrease in blood microfilariae (See Clinical efficacy and safety section below).

Clinical efficacy and safety

The efficacy of diethylcarbamazine citrate was first established as a 12-day treatment for lymphatic filariasis; however meta-analysis across studies has indicated that a single dose is as effective as a 12-day treatment regimen in clearance of microfilariae from the blood. Decrease in blood microfilariae is the standard measure of efficacy in lymphatic filariasis.

The improved efficacy of two-drug regimens in treating subjects with microfilariae supported the use of diethylcarbamazine citrate and albendazole in single-dose, once-yearly treatment to reduce microfilaraemia in endemic populations and this is one of the regimens used in the MDA programmes.

The effectiveness of MDA programmes has been demonstrated in studies conducted in India, Papua New Guinea, Vanuatu and Egypt. For example, the Ramaiah KD et al., 2011 study suggests that six rounds of once-yearly mass administration of single doses of diethylcarbamazine citrate and albendazole, with 60% to 70% treatment coverage, is likely to achieve total interruption of transmission and elimination of lymphatic filariasis in the majority of villages. An efficacy summary of the microfilariae clearance observed in several field studies in the MDA programmes is presented in the following table:

MDA programmes*				
Study	**Treatment Arm**	**Number of Subjects**	**Microfilaraemia**	
			Baseline	**Endpoint**
Ramaiah KD et al., 2011 Five villages (South India)	6 mg/kg DEC plus 400 mg ALB	5622 60% to 70% of the eligible population (>15 kg body weight)	Baseline Mf prevalence rate ranged from 4.27% (10/234) to 11.36% (5/44) in the 5 study villages; the overall prevalence was 8.10% (63/778) (CI: 6.18 to 10.01).	**After 6 rounds of MDA:** Overall prevalence fell to 1.01% (8/791) (CI: 0.31 to 1.71), equivalent to microfilaraemia clearance rate of 88%. The Mf prevalence fell to <0.5% in 4 of the 5 villages and it was 2.93% (6/205) in the fifth village. Two villages achieved 0% prevalence after the fourth round of MDA and maintained the same level thereafter. Reduction in Mf prevalence ($P < 0.05$)
Weil GJ et al., 2008 Four villages (Papua New Guinea)	6 mg/kg DEC plus 400 mg ALB	971 to 1000 per cycle (compliance of 72.9%)	**After 3 rounds of MDA:** Mf clearance rates in infected persons were 76%, 95.2%, and 98.1% after 1, 2, and 3 rounds of MDA, respectively. $P = 0.013$ The difference in baseline Mf counts between the two groups was statistically significant ($P < 0.001$).	**After 3 rounds of MDA:** Mf clearance rates in infected persons were 76%, 95.2%, and 98.1% after 1, 2, and 3 rounds of MDA, respectively. $P = 0.013$ The difference in baseline Mf counts between the two groups was statistically significant ($P < 0.001$).
Rajendran R et al., 2006 Two communities (South India)	6 mg/kg DEC plus 400 mg ALB 6 mg/kg DEC alone	DEC plus ALB: 703 to 1724 per cycle (coverage of 72.7%-94.4%; compliance of 52.4%-83.6%) DEC alone: 827 to 1432 per cycle (coverage of 67.9%-98.9%; compliance of 42.4%-80.3%)	The Mf prevalence in the 2 to 25 years age group was 5.21% in DEC plus ALB arm and 4.34% in DEC alone arm	**After 3 rounds of MDA:** The percentage reductions in Mf prevalence were higher in the DEC plus ALB arm (72.4% versus 51.4%). $P < 0.05$ in both arms.
Ramzy RM et al.,2006 Four villages (Egypt)	6 mg/kg DEC plus 400 mg ALB	Approx 1800	Microfilaraemia prevalence rates were much higher in Giza than in Qalubyia (11.5 [95% CI: 10.2 to 12.8] and 3.1 [95% CI: 2.4 to 3.8], respectively).	**After 5 rounds of MDA:** In Giza, prevalence rates of microfilaraemia fell from 11.5% to 1.2%. In Qalubyia, prevalence rates of microfilaraemia fell 13.6% to 3.1%. $P < 0.0001$ in both Giza and Qalubyia

Fraser M et al., 2005 Eight sentinel sites (Vanuatu)	100 to 400 mg DEC (depending on age) plus 400 mg ALB	561 (average of 72% of the eligible population)	**Baseline:** Microfilaraemia prevalence was 12%	**After 2 rounds of treatment:** Prevalence of microfilaraemia was reduced by 93% (from 12% to 0.8%) Reduction in prevalence of microfilaraemia ($P < 0.001$)

*Studies used various formulations of Diethylcarbamazine.

5.2 Pharmacokinetic properties

Absorption and bioavailability

Diethylcarbamazepine is readily absorbed following oral administration. Bioavailability is between 80 and 85%. Following single dose administration of one Diethylcarbamazine tablet in healthy volunteers in the fed state, the mean (±SD) diethylcarbamazepine Cmax value was 598 (±84) ng/ml and the corresponding value for AUC was 7950 (±1660) ng.h/ml. The mean (±SD) diethylcarbamazepine Tmax value was 2.25 (± 1.17) hours.

Distribution

Diethylcarbamazine is widely distributed in tissues and is mainly excreted in the urine unchanged and as the metabolite, diethylcarbamazine N-oxide. Urinary excretion, and hence plasma half–life, is dependent on urinary pH. About 5% of a dose is excreted in the faeces.

Metabolism

In rats and monkeys after an intravenous dose, 10-20% is excreted in the urine as unchanged drug, most of which is excreted in the first 3 hours. Metabolites more slowly eliminated include N-ethyl-4-methyl-1-piperazine-carboxamide (MEC) and their N-oxides, 4-methyl-piperazine-carboxamide and N,N-diethyl-1-piperazine-carboxamide. In vivo most of the metabolites are active on microfilariae and both N-oxides active on adults and infective larvae. The antifilarial action of DEC is swift and of short duration. This action is prolonged by the activity of metabolites, especially the N-oxides.

Elimination

Diethylcarbamazine elimination is primarily through renal clearance, which accounts for around 50% of the total plasma clearance. The remaining clearance is via metabolism, leading to a number of metabolites, which are also renally cleared. Given that the major elimination pathway is renal clearance and that metabolic clearance is via several routes, genetic polymorphisms of drug metabolizing enzymes are very unlikely to have any clinically relevant consequences. This is borne out by the fact that there are no reported significant drug-drug interactions with Diethylcarbamazine citrate which would likely be evident if modulation of metabolic clearance was an important factor in determining systemic exposure.

The PK of Diethylcarbamazine citrate was not altered by timing of administration (morning versus evening).

The elimination half-life and area under the plasma concentration-time curve of Diethylcarbamazine were significantly increased when an alkaline urinary pH was maintained compared with the values of these parameters obtained on a second occasion when an acidic urinary pH was maintained. This effect is unlikely to be of clinical relevance in the MDA program.

Renal impairment

Results in patients with chronic renal impairment and in healthy subjects given a single 50 mg oral dose of Diethylcarbamazine indicated that the plasma half–life of Diethylcarbamazine is prolonged and its 24-hour urinary excretion is considerably reduced in those with moderate to severe renal impairment. No significant correlations were observed between age, sex or weight and renal function, but Diethylcarbamazine excretion did appear to decrease with increasing urinary pH.

5.3 Preclinical safety data

Nonclinical studies have not been performed with Diethylcarbamazine Citrate Tablets. However, Diethylcarbamazine citrate is a well-established drug with an extensive record of clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose,
Maize Starch,
Methyl Paraben,
Propyl Paraben,
PVPK-30,
Purified Talc,
Sodium Starch Glycollate,
Magnesium Stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store in a cool place and dry place .Protect from light. Keep all medicines out of reach of children.

6.5 Nature and contents of container

1000 tablets sealed in a printed PP bag and packed in 350ml White colour container with 2silica and one literature.

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT/MANUFACTURER

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