SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NOTEZINE 100 mg, scored tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diethylcarbamazine citrate ..... 196.4 mg

(equivalent to diethylcarbamazine ..... 100.0 mg)

For one scored tablet weighing 300 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Scored tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of filariasis caused by *Wuchereria bancrofti, Brugia malayi, Brugia timori, Loa loa, Onchocerca volvulus*.

4.2. Posology and method of administration

Oral use.

NB: the doses are expressed as diethylcarbamazine base.

A daily dose of 400 mg of diethylcarbamazine base should not be exceeded.

Treatment of lymphatic filariasis (*Wuchereria bancrofti, Brugia malayi*, *Brugia timori*):

Treatment should preferably be administered in divided doses, after meals.

Individual treatment: 3 mg/kg/day of diethylcarbamazine base for 12 to 14 consecutive days. The course may be repeated, if necessary, after a minimum interval of 10 days.

Mass treatment: a single annual dose of 3 mg/kg of diethylcarbamazine base, combined with another anthelmintic (please refer to the WHO recommendations).

Occult filariasis (tropical pulmonary eosinophilia):

3 mg/kg/day of diethylcarbamazine base for 14 to 21 days. The course of treatment can be repeated if symptoms reappear.

Loiasis (infestation by Loa loa):

The treatment should be started under strict medical supervision. The higher the numbers of microfilariae in the blood, the lower the dose of diethylcarbamazine base(3 mg). For example:

- 1st day: 1/32 of a tablet (the dilution should be carried out by a pharmacist);
- the dose should be doubled on subsequent days, until an effective daily dose of 3 mg/kg of diethylcarbamazine base is reached after one week, taken as 2 divided doses.

The effective dose should be maintained over 21 days.

Corticosteroids can be given along with diethylcarbamazine to minimise or prevent adverse reactions (see section 4.4).

Onchocerciasis (infestation by *Onchocerca volvulus*):

To limit the occurrence of adverse reactions to the treatment (Mazzotti reaction), the treatment can be started at low, progressively increasing doses.

For example:

- Day 1: 0.5 mg/kg of diethylcarbamazine base as a single dose;

- depending on the patient's clinical condition, the dose can be doubled on subsequent days until an effective dose of 3 mg/kg/day, divided into two daily amounts, is reached. The effective dose should be continued for approximately 10 days.

To attenuate or prevent adverse reactions, corticosteroid therapy (0.5 mg/kg in prednisolone equivalent) may be combined with diethylcarbamazine (see section 4.4).

4.3. Contraindications

- hypersensitivity to one of the ingredients.
- severe eye disease in the context of onchocerciasis.
- gluten intolerance, due to the presence of wheat starch (gluten).

4.4. Special warnings and precautions for use

The intensity and severity of undesirable effects after administration of diethylcarbamazine are related to the microfilaria blood load before treatment. In cases of infestation by *Loa loa*, the blood level of microfilaria is usually high, which leaves patients who have been treated predisposed to an increased risk of serious adverse reactions. Severe central neurological disturbances, such as encephalopathy and coma, have been described, particularly in patients with *Loa loa i*nfestation who are treated with diethylcarbamazine. These reactions can be attenuated or prevented by starting with a progressive dosage and adding corticosteroids.

The appearance of skin and/or systemic reactions of variable severity (Mazzotti reaction) and eye reactions has been described following the administration to onchocerciasis patients of medicinal products with a rapid microfilaricidal action, such as diethylcarbamazine. These manifestations are probably related to an inflammatory process triggered following the death of the microfilaria and the release of degradation products. These reactions can be attenuated or prevented by starting with a progressive dosage and adding corticosteroids.

Mass treatment with diethylcarbamazine is not recommended in countries where onchocerciasis is endemic.

There is no evidence to justify the use of diethylcarbamazine as individual prophylaxis for infestation by filaria.

Diethylcarbamazine must be used with caution in patients with a history of convulsions or factors predisposing to the occurrence of convulsions.

In patients with renal impairment, urinary excretion is reduced and the elimination half-life is increased according to the degree of renal function impairment. Consequently, the doses should be adjusted in these patients.

In children, diethylcarbamazine must always be administered under strict medical surveillance and in divided daily doses.

In cases with a concomitant acute disorder, it is preferable to wait for the patient to recover before using diethylcarbamazine.

This medicinal product contains lactose. Its use is not advisable in patients with congenital galactosemia, glucose or galactose malabsorption syndrome or lactase deficiency.

4.5. Interaction with other medicinal products and other forms of interaction

Not applicable.

4.6. Pregnancy and lactation

Pregnancy

Studies conducted in animals have not demonstrated any teratogenic effects. In the absence of teratogenic effects in animals, malformation in humans is not expected.

Substances responsible for malformations in humans have, to date, proved teratogenic in animals during correctly conducted studies in two species.

There are currently no relevant data available on possible malformations or foetal toxic effects due to diethylcarbamazine when it is administered during pregnancy.

Consequently, as a precaution, this medicinal product should preferably not be used during pregnancy.

Breast-feeding

In the absence of studies, the administration of diethylcarbamazine is not recommended during lactation.

4.7. Effects on ability to drive and use machines

Vehicle drivers and machine users should be informed of the risk of drowsiness related to using this medicinal product.

4.8. Undesirable effects

The adverse reactions are variable depending on the underlying parasitosis.

Treatment of onchocerciasis:

The administration of diethylcarbamazine in patients with *Onchocerca volvulus* infestation may cause a secondary inflammatory reaction known as a Mazzotti reaction, from the first dose. This is triggered following the death of the microfilaria and the release of degradation products. Its intensity depends on the dose of the medicinal product and the filarial load.

The filaria are usually located in the skin but can spread to the eyes and are sometimes severe and generalized in severely infested individuals.

- Skin reaction: 1 to 24 hours after administration, pruritus, urticarial rash and oedema are observed which, depending on the distribution of the filaria, remain localised or extend to the whole body. Painful adenitis and lymphangitis appear.

  Patients with hyperreactive onchocerciasis dermatitis or “Sowda” (observed in Yemen in particular) seem to develop severe skin reactions (oedema, aggravation of dermatitis, etc.) more frequently after microfilaricidal treatment.

- Eye reaction: when the microfilaria are contained in the conjunctiva, cornea or anterior chamber of the eye, lacrimation, photophobia, conjunctivitis or acute iridocyclitis may be observed. Oedema affecting the cornea and raised intraocular pressure in a massively parasitised individual may require specialised treatment and surveillance. The prolonged use of diethylcarbamazine is sometimes associated with inflammatory and then degenerative alterations of the optic nerve and retina, which can cause narrowing of the visual field.

- Systemic reaction: orthostatic hypotension, collapse, respiratory distress, vertigo, fever, arthralgia, myalgia, and headaches have been described. These manifestations can be intense and persist for several days.

Treatment of lymphatic filariasis and loiasis:

Secondary reactions resembling the Mazzotti reaction described in onchocerciasis victims have been described during the treatment of lymphatic filariasis, or loiasis. The incidence and severity of the reactions depend on the microfilaraemia and dose of diethylcarbamazine administered. Fever, headaches, vertigo, anorexia, feeling unwell, urticaria, vomiting and asthma attacks may appear within a few hours of the administration of the first dose of diethylcarbamazine. These effects generally disappear by the 5th day of treatment at the latest. Reversible proteinuria may also be observed.

Cases of meningoencephalitis have been described in patients with massive *Loa loa* microfilaraemia.

During the treatment of lymphatic filariasis, the death of the adult worms causes the formation of palpable nodules in the subcutaneous tissue and along the spermatic cord. Localised oedema, inflammation around the vessels, transient lymphangitis and lymphoedema may appear.

Isolated cases of convulsions have been described in patients with a history of epilepsy.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system : French national Agency for the Safety of Medicinal and Health Products (ANSM) and the network of Regional Pharmacovigilance Centers - Website: www.ansm.sante.fr.

4.9. Overdose

Symptoms: nausea, vomiting, headaches, vertigo, drowsiness and, in severe cases, convulsions.

Procedure: medical surveillance and symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: ANTHELMINTICS (P: Parasitology)

Diethylcarbamazine is a piperazine derivative with microfilaricidal action. Diethylcarbamazine acts on *Loa loa* macrofilaria.

5.2. Pharmacokinetic properties

Diethylcarbamazine is absorbed almost completely by the oral route and diffuses widely into non-fatty tissues. Its metabolisation is rapid and extensive, the residual fraction being recovered unchanged in the urine in the subsequent 48 hours. The plasma half-life is generally approximately 6 to 12 hours.

5.3. Preclinical safety data

Not stated.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Wheat starch, lactose monohydrate, colloidal hydrated silica, magnesium stearate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

5 years.

6.4. Special precautions for storage

No special storage conditions.

6.5. Nature and contents of container

Blister (PVC/aluminium) of 10 scored tablets.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

SANOFI-AVENTIS FRANCE

1-13, boulevard Romain Rolland

75014 PARIS

FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

307 391-0: 20 scored tablets in (PVC/aluminium) blisters.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[to be completed later by the MA holder]

10. DATE OF REVISION OF THE TEXT

[to be completed later by the MA holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR PRESCRIPTION AND SUPPLY

Medicinal product not subject to medical prescription.