1. NAME OF THE MEDICINAL PRODUCT
Avrozole Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Albendazole 200mg

3. PHARMACEUTICAL FORM
Tablet

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Avrozole is a broad spectrum anthelminthic indicated for the treatment of single and mixed infections due to:

- Round worm (ascariasis)
- Thread worm or pinworm (enterobiasis)
- Hookworm
- Whip worm (trichuriasis)
- Tapeworm (strongyloidiasis, cysticercosis and echinococcosis i.e hydatid disease)
- Intestinal nematodes (capilliariasis and trichostrongyliasis).
- Tissue nematode infections (cutaneous larva migrans, toxocariasis, trichinosis and gnasthostomiasis).
- Filarial nematode infection (in combination with diethylcarbamazine or ivermectin).

4.2 Posology and method of administration

Single and mixed intestinal nematode infections:

(Ascariasis, enterobiasis, hook worm, strongyloidiasis and trichuriasis)
Adults and children above 2 years: single dose of 400mg (2 tablets or 20ml suspension)

Children 1 - 2 years: single dose of 200mg (1 tablet or 10ml suspension)
The dose may be repeated in 1 to 4 weeks for enteriobiasis (thread worm or pin worm infection).

Tape worm infections:
Echinococcosis (Hydatid disease)
Adults over 60kg: 400mg (2 tablets or 20ml suspension) twice daily with meals for 28 days. The 28-day course is repeated after 14 days without treatment to a total of 3 treatment cycles.

Less than 60kg (Children from 2 years): 7.5mg/kg twice a day to a maximum total daily dose of 800mg (40ml suspension) for 28 days. The 28-day course is repeated after 14 days without treatment to a total of 3 treatment cycles.

Cysticercosis (larval tape worm infection)
Adults over 60kg: 400mg (2 tablets or 20ml suspension) twice daily for 8-30 days

Less than 60kg: 15mg/kg daily given in divided doses twice a day to a maximum total daily dose of 800mg (40ml suspension) for 8-30 days.

Strongyloidiasis:
Adults and children above 2 years: 400mg (2 tablets or 20ml suspension) 1 to 2 times daily for 3 consecutive days. This may be repeated after 3 weeks if necessary.

Capillariasis:
Adults and children above 2 years: 400mg (2 tablets or 20ml suspension) daily for 10 days.

Cutaneous larva migrans:
Adults and children above 2 years: 400mg (2 tablets or 20ml suspension) daily for 3 to 4 days.

* For children under 6 years, tablet form of 400 mg is inappropriate due to wrong route risk, and

only suspension form should be used.
**If the worm control performed 3 weeks after the treatment is positive, a second treatment should be administered.

Special populations

Elderly people: Data concerning patients from 65 years old are limited. Reports suggest that no adaptation of the posology is required in elderly people. However, albendazole should be used with care in patients with a liver dysfunction.

Liver failure: Albendazole is rapidly metabolized by the liver, the main metabolite, albendazole sulfoxide, is pharmacologically active. Hence, liver failure might result in significant effect on the pharmacokinetics of albendazole sulfoxide. Patients with abnormal liver function tests (transaminases) prior to treatment with albendazole should be closely monitored. The treatment should be stopped in case of significant increase in liver enzymes or in case of clinically significant decrease in blood formula numeration (see section 4.4).

Renal failure:
As the elimination of albendazole and its main metabolite, albendazole sulfoxide are negligible, it is unlikely that the clearance of these compounds are modified in patients with renal failure. No dose adaptation of posology is required, however, patients with renal failure should be closely monitored.

4.3 Contraindications
- Hypersensitivity to Albendazole, or to similar medications such as Mebendazole.
- Liver disease or patients with abnormal liver function tests.
- Pregnancy or if you are planning to become pregnant
- during breast-feeding.
- Children weighing less than 15kg.

4.4 Special warnings and precautions for use
Neurologic symptoms A treatment with albendazole might reveal a pre-existing neurocysticercosis, in particular in regions of strong infestation with taeniasis. Patients might feel neurological symptoms such as convulsions, increase in intracranial pressure and focal signs resulting from the inflammatory reactions following the death of the parasite in the brain. Symptoms might appear shortly after the treatment; an adapted treatment with corticoids and anticonvulsants should be immediately started.

Precaution for use when using albendazole for systemic infections (long-term treatment with higher doses):

Liver disorders: Albendazole might result in a slight to moderate increase in liver transaminases, normalising generally when stopping the treatment. Serious cases of hepatitis have also been reported when treating systemic helminth infections (long-term treatment with higher doses) (see section 4.8). Tests of the liver function should be carried out prior to starting the treatment and at least every second week during the treatment. Albendazole shall be stopped in case of increase in hepatic enzymes (more than twice normal). If reintroducing the treatment is indispensable, this should be done after normalisation of liver enzymes. Moreover, a close monitoring should be carried out, keeping in mind that potential relapses might appear because an allergic mechanism cannot be discarded.

Medullar depression: Cases of medullar depression have been reported during treatment of systemic helminth infections (longterm treatment with higher doses) (see section 4.8). Numerations of blood formula should be performed when starting the treatment and then after two weeks of treatment with albendazole. Patients with a liver disease, including liver echinococcosis, seem more likely to develop a medullar depression, leading to pancytopenia, medullar aplasia, agranulocytosis and leucopoenia. Then, an increase monitoring of the blood formula is recommended in patients showing a liver disease. Albendazole shall be stopped in case of significant decrease in the number of blood cells (see section 4.2 and 4.8). In the treatment of trichinosis, few data are available with

albendazole in children under 6 years of age. In the treatment of trichinosis, because of the activity, in particular on the intestinal forms and of the larvae in the early phase of the tissue migration, it is recommended to administer albendazole as early as possible at the start of the infestation in order to decrease the symptoms and the complications. This treatment remains inactive on the encysted larvae in chronic forms and when it is initiated belatedly.

Contraception: Before initiating the treatment with albendazole, the doctor should inform the patient of the embryotoxic, teratogenic and aneugenic risks of albendazole, of the necessity of an efficient contraception and of the 5 potential consequences on pregnancy if it occurs during the course of the treatment with albendazole (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction
Enzymes inducers anticonvulsivants, ritonavir and rifampicine may have the potential to reduce plasma concentrations of albendazole and of its active metabolite, albendazole sulfoxide with a risk of decrease in its efficacity. Clinical monitoring of the therapeutic efficacy and the potential adaptation of the posology of albendazole during the course of the treatment with an enzymatic inducer and after stopping.

Praziquantel has increased the plasma concentration of albendazole sulfoxide.

Phenytoin, carbamazepine and phenobarbital appear to induce the oxidative metabolism of albendazole via the cytochrome P450 isoenzyme CYP3A by roughly the same extent, resulting in significantly reduced concentrations of albendazole sulfoxide.

Plasma concentrations of albendazole sulfoxide were reported to be raised by about 50% in a study in 8 patients receiving dexamethasone.

Concentrations of albendazole sulfoxide have been found to be raised in bile and hydatid cyst fluid when albendazole was given with cimetidine which may increase efficacy in the treatment of echinococcosis.

4.6 Fertility, Pregnancy and lactation
Female patients
Given the aneugenic, embryotoxic and teratogenic potential of albendazole, all the precautions should be taken in order to avoid pregnancy in these female patients. Treatment with albendazole should not be initiated before a negative result to a pregnancy test performed right before the treatment initiation. Women of childbearing age should use an efficient contraceptive method during the treatment and 6 months after stopping the treatment.

Male patients and their female partners
All precaution should be taken in order to avoid pregnancy in the partners of male patients treated with albendazole. It is not known if the presence of albendazole in sperm can cause teratogenic or genotoxic effects on human embryo/foetus. Men or their female partners of childbearing age must be informed of the obligation to use an efficient contraceptive method during all the course of the treatment with albendazole and during 3 months after stopping the treatment. Men whose partners are pregnant should be informed of the obligation to use a condom in order to reduce the exposition of their partner to albendazole.

Pregnancy
Studies in animal showed teratogenic embryotoxic effects in rat and rabbit at doses close to those used in men (see section 5.3). in clinical trials, the data on the use of albendazole during the first term of pregnancy are limited. Albendazole is contraindicated during pregnancy (see section 4.3 and 4.4), espacially because there are therapeutical alternatives that are better assessed in terms of safety in pregnant woman. Female patients should be informed of the necessity to consult their doctor immediately in case of pregnancy. This is based on prenatal monitoring targeted on malformations described in animal (skeletic, cranofacial, limbs).

Fertility In rat or mouse, studies have showed testicular toxicity of albendazole (see section 5.3). albendazole has an aneugic activity, which is a risk factor for alteration of fertility in man.

Breastfeeding
Albendazole is present in human breast milk after a single dose of 400 mg. Because of its aneugenic activity, a risk for the new born child cannot be excluded. In case of a single dose, breastfeeding should be stopped at the time of intake and for at least 5.5 half-lives (about 48 hours) after stopping the treatment. Before initiatiing breastfeeding, pump all the available breask milk and dispose of it; in case of repeated intakes, breastfeeding is contraindicated.

4.7 Effects on ability to drive and use machines
When driving or using machines, it should be kept in mind that dizziness have been reported after using albendazole (see section 4.8).

4.8 Undesirable effects
The frequency of side effects very common to rare have been determined based on the data from the clinical trials. The frequencies of the other side effects are mainly based on the post-marketing data and are referred to the reported observations rather than the real frequencies.
The side effects listed below are classified by organ system and frequency, according to the following convention:
Very common ≥ 1/10
Common ≥ 1/100 to < 1/10
Uncommon ≥ 1/1,000 to < 1/100
Rare ≥ 1/10,000 to < 1/1,000
Very rare < 1/10,000
Unknown frequency (cannot be estimated based on the available data).

Intestinal and skin infections (short term treatment with low doses)

Systemic Class Organ	Uncommon	Unknown Frequency
Immune System Disorders		Hypersensitivity reaction, including skin rash, itching and hives
Nervous System Disorders	Headache, Dizziness(see section 4.7)	
Gastro-intestinal Disorders	Gastro-intestinal symptoms (epigastric or abdominal pains, nausea, vomiting) and diarrhoea	
Hepatobiliary Disorders		Increase in liver Enzymes(see section 4.4)
Skin and Cutaneous tissue Disorders		Polymorphic erythema, Stevens-Johnson Syndrome.

Systemic Infections (long term treatment with higher doses)

Systemic Class Organs	Very Common	Common	Uncommon	Unknown Frequency
Haematological and Lymph system disorders				Medullar aplasia, leucopoenia, pancytopenia, agranulocytosis (see section 4.4)
Immune System Disorders			Hypersensitivity reactions including skin rash, itching, hives	
Nervous System Disorders	Headaches	Dizziness(see section 4.7)		
Gastro-intestinal Disorders			Gastro-intestinal disorders(abdomina	

			l pains , nausea and vomiting)	
Hepatobiliary Disorders	Slight to moderate increase in liver enzymes(see section 4.4)		Hepatitis (see section 4.4)	
Skin and subcutaneous tissue Disorders		Reversible alopecia(decrease in thickness of the hair, moderate hair loss)		Polymorphic erythema, Stevens-Johnson Syndrome
General Disorders and Administration site conditions		Fever		

4.9 Overdose
Large doses are reported to cause diarrhoea and gastro intestinal disturbances, which are mild, transient and not requiring the withdrawal of drug.
In case of overdose, symptomatic treatment and medical monitoring are recommended.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antiparasitics - antihelmintics, ATC code: P02CA03.

Albendazole is a benzimidazole carbamate. Albendazole is broad-spectrum antihelmintics, which is effective against a wide range of intestinal helminths. Albendazole acts on helminths'cytoskeleton by the inhibition of tubulin polymerisation and thus, their introduction in the microtubules, blocking glucose absorption of parasites and resulting in their death. Albendazole is also active on Giardia intestinalis (or duodenalis). It has an irreversible action that is targeted on the ventral disc of the trophozoites by acting on the polymerisation of tubulin and giardine, leading to a disorganisation of the cytoskeleton and micro strips. The ability of adhesion to the enterocytes is decreased, resulting in an inhibition of the growth and multiplication of the parasite.

5.2 Pharmacokinetic properties
Absorption and biotransformation

Following the administration, the low proportion of albendazole is absorbed (< 5 %) is metabolised into
albendazole sulfoxide and sulfone. The plasma concentration in sulfoxide, the main active circulating metabolite reaches its maximum about two and a half hours after its administration.
The systemic pharmacological effect of albendazole is increased if the dose is administered concomitantly with a fat-rich meal, improving absorption by about 5.

Elimination
The plasma half-life of albendazole sulfoxide is 8 and a half hours.
Albendazole sulfoxide and its metabolites seem to be mainly eliminated by biliary route and for a lower
proportion by urinary route.

Specific population
Renal failure: albendazole pharmacokinetics has not been studied in patients with renal failure.
Haptic failure: albendazole pharmacokinetics has not been studied in patients with hepatic failure.

5.3 Preclinical safety data
No further information of relevance to add.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium Starch Glycolate
Magnesium Stearate
Maize Starch
Povidone K.30
Docusate Sodium
Avicel PH 101

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 30°C. Protect from light

6.5 Nature and contents of container
Avrozole Tablets is available in ALU-PVC blister packs of 1 x 2 and 15 x 2 tablets

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local Requirements

7. APPLICANT/MANUFACTURER
Avro Pharma Limited
Daid House, Plot 2, Block J, Limca Way,
Isolo Industrial Estate, Oshodi-Apapa Expressway
Isolo, Lagos State.
Tel: +234(1)2913955
Email: avropharma@yahoo.com