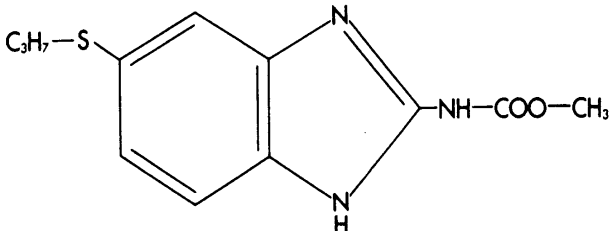
ZENTEL® (Albendazole) PRODUCT INFORMATION

DESCRIPTION

ZENTEL contains albendazole, which is methyl [5-(propylthio)-1H-benzimidazol-2-yl] carbamate. It is a member of the benzimidazole group of anthelmintic agents.



Albendazole is a white to off-white, odourless or almost odourless powder, which is practically insoluble in water and slightly soluble in methanol, chloroform, ethyl acetate and acetonitrile. Its molecular weight is 265.33.

PHARMACOLOGY

ZENTEL (albendazole) is a broad-spectrum anthelmintic, which is highly effective against a wide range of intestinal helminths. ZENTEL is also effective against tissue helminth infections, such as cutaneous *larva migrans* (see INDICATIONS).

Albendazole therapy has also been used in the high dose, long term treatment of tissue helminth infections including hydatid cysts and cysticercosis.

The antihelminthic action of albendazole is thought to be mainly intra-intestinal. However, at higher albendazole doses, sufficient is absorbed and metabolised to the active sulphoxide metabolite, to have a therapeutic effect against tissue parasites.

Albendazole exhibits larvicidal, ovicidal and vermicidal activity, and is thought to act via inhibition of tubulin polymerization. This causes a cascade of metabolic disruption, including energy depletion, which immobilizes and then kills the susceptible helminth.

Pharmacokinetics

In man, the full extent of albendazole absorption following oral administration has not been established. However, it is known that albendazole is poorly absorbed with most of an oral dose remaining in the gastrointestinal tract. The poor absorption is believed to be due to the low aqueous solubility of albendazole. Absorption is significantly enhanced (approximately 5 fold) if albendazole is administered with a fatty meal.

Albendazole rapidly undergoes extensive first-pass metabolism in the liver, and is generally not detected in plasma. Albendazole sulphoxide is the primary metabolite, which is thought to be the active moiety in effectiveness against systemic tissue infections. The plasma half life of albendazole sulphoxide is 8½ hours. Albendazole sulphoxide and its metabolites appear to be principally eliminated in bile, with only a small proportion appearing in the urine.

INDICATIONS

Single dose or short term courses of ZENTEL are indicated in the treatment of single or mixed infestations of intestinal and tissue parasites, in adults and children over 2 years of age.

Clinical studies have shown ZENTEL to be effective in the treatment of infections caused by:

Enterobius vermicularis (pinworm/threadworm), *Ascaris lumbricoides* (roundworm), *Ancylostoma duodenale* and *Necator americanus* (hookworms), *Trichuris trichiura* (whipworm), *Strongyloides stercoralis*, animal hookworm larvae causing cutaneous *larva migrans,* and the liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis*.

ZENTEL is also indicated for the treatment of *Hymenolepis nana* and *Taenia* spp. (tapeworm) infections, when other susceptible helminths species are present. Treatment courses should be extended to 3 days (see WARNINGS AND PRECAUTIONS).

CONTRAINDICATIONS

ZENTEL should not be administered during pregnancy or in women thought to be pregnant. ZENTEL has been shown to be teratogenic and embryotoxic in rats and rabbits. Women of childbearing age should be advised to take effective precautions against conception during and within one month of completion of treatment with ZENTEL (see Use in Pregnancy, Category D).

ZENTEL is contraindicated in persons who are known to be hypersensitive to albendazole, other benzimidazole derivatives, or any component of the tablets.

PRECAUTIONS

Use in Systemic Helminth Infections (longer duration of treatment at higher doses)

Mild to moderate elevations of liver enzymes have been reported with albendazole. In prolonged higher dose albendazole therapy for hydatid disease there have been rare reports of severe hepatic abnormalities associated with jaundice and histological hepatocelluler damage, which may be irreversible. Enzyme abnormalities usually normalise on discontinuation of treatment.

Patients with abnormal liver function test results (transaminases) prior to commencing albendazole therapy should be carefully evaluated and therapy should be discontinued if liver enzymes are significantly increased (greater than twice the upper limit of normal) or full blood count decreased by a clinically significant level (see Adverse Reactions). Albendazole treatment may be restarted when liver enzymes have returned to normal limits, but patients should be carefully monitored for a recurrence.

Case reports of hepatitis have also been received (see Adverse Reactions). Liver function tests should be obtained before the start of each treatment cycle and at least every two weeks during treatment.

Albendazole has been shown to cause bone marrow suppression and therefore blood counts should be performed at the start and every two weeks during each 28 day cycle. Patients with liver disease, including hepatic echinococcosis, appear to be more susceptible to bone marrow suppression leading to pancytopenia, aplastic anaemia, agranulocytosis and leukopenia and therefore warrant closer monitoring of blood counts. Albendazole should be discontinued if clinically significant decreases in blood cell counts occur.

Symptoms associated with an inflammatory reaction following death of the parasite may occur in patients receiving albendazole treatment for neurocysticercosis (e.g. seizures, raised intracranial pressure, focal signs). These should be treated with appropriate steroid and anticonvulsant therapy. Oral or intravenous corticosteroids are recommended to prevent cerebral hypertensive episodes during the first week of treatment.

Pre-existing neurocysticercosis may also be uncovered in patients treated with albendazole for other conditions, particularly in areas with high taenosis infection. Patients may experience neurological

symptoms e.g. seizures, increased intracranial pressure and focal signs as a result of an inflammatory reaction caused by death of the parasite within the brain. Symptoms may occur soon after treatment, appropriate steroid and anticonvulsant therapy should be started immediately.

There is a risk that treatment of *Taenia solium* infections may be complicated by cysticercosis, and appropriate measures should be taken to minimise this possibility.

Confirmation of eradication of many intestinal and tissue parasites is necessary after treatment. (see DOSAGE AND ADMINISTRATION)

Use in Impaired Renal or Hepatic Function

The use of ZENTEL in patients with impaired renal or hepatic function has not been studied. However, caution should be used in patients with pre-existing liver disease, since ZENTEL is metabolised by the liver and has been associated with idiosyncratic hepatotoxicity.

Use In Children

There is limited experience with ZENTEL in children under 2 years of age, therefore use in this age group is not recommended.

Carcinogenicity and Mutagenicity

No evidence of carcinogenic activity was observed in mice given albendazole in the diet at doses up to 400mg/kg/day for 25 months. In rats, dietary administration of doses of 3.5, 7 and 20mg/kg/day did not affect the total incidence of adrenocortical tumours (adenoma plus carcinoma), however, in females there was an increased incidence of adrenocortical carcinomas.

Mutagenicity tests with bacterial cells and an assay of chromosomal damage *in vivo* have shown no clear evidence that albendazole has genotoxic activity. A cell transformation assay showed a slight dose-related increase in the transformation rate of cultured mouse cells in the presence of metabolic activation.

Use in Pregnancy (Category D)

See CONTRAINDICATIONS. ZENTEL is contraindicated during pregnancy, and for one month prior to conception. In order to avoid administering albendazole during early pregnancy, women of child bearing age should initiate treatment during the first week of menstruation or after a negative pregnancy test.

The use of ZENTEL in human pregnancy has not been studied, but in animal studies it is teratogenic in more than one species. In animal studies oral treatment with maternotoxic doses of albendazole (30mg/kg/day) during the period of organogenesis was associated with multiple malformations in rats and ectrodactyly in rabbits. In one study in rats, an oral dose (10mg/kg/day) similar to the human therapeutic dose was not maternotoxic, but was associated with microphthalmia and microfetalis. The latter occurred alone and together with multiple malformations including cranioschisis, talipes and renal agenesis. There is no information on the possible effect of albendazole on the human foetus.

Use in Lactation:

Adequate human and animal data on use during lactation are not available. Therefore breast feeding should be discontinued during and for a minimum of 5 days after treatment.

Interactions

Cimetidine, praziquantel and dexamethasone have been reported to increase the plasma levels of the albendazole active metabolite.

Ritonavir, phenytoin, carbamazepine and phenobarbital may have the potential to reduce plasma concentrations of the active metabolite of albendazole; albendazole sulfoxide. The clinical relevance of this is unknown, but may result in decreased efficacy, especially in the treatment of systemic helminth infections. Patients should be monitored for efficacy and may require alternative dose regimens or therapies.

ADVERSE REACTIONS

The following adverse events were observed during clinical studies. It should however be noted that causality has not necessarily been established for these events.

Common (≥1%)

Abdominal pain was the most frequently reported symptom (1%) during short term dosing, however this frequency was not significantly different from that in placebo-treated patients.

Uncommon (>0.1% and <1%)

Diarrhoea, nausea, vomiting, dizziness, itchiness and/or skin rashes were reported. There was no significant difference in the percentage of patients experiencing diarrhoea, compared to placebo-treated patients.

Rare (< 0.1%)

Rarely reported events included bone pain, proteinuria, and low red cell count. Leucopenia and transiently raised hepatic enzymes were reported in studies with laboratory monitoring, however no definite relationship to the drug was shown.

Hypersensitvity reactions including rash, pruritis and urticaria have been reported very rarely.

During prolonged higher dose albendazole therapy of hydatid disease there have also been reports of severe hepatic abnormalities, including jaundice and hepatocellular damage which may be irreversible.

Post-Marketing Data

During post-marketing surveillance, the following reactions have been reported additionally in temporal association with ZENTEL.

Use in intestinal infections and Cutaneous *larva migrans* (short duration treatment at lower dose):

Headache has been reported uncommonly (≥ 0.1% and <1%) in treatment with albendazole.

Erythema multiforme and Stevens-Johnson syndrome have been reported very rarely (<0.01%).

Use in systemic helminth infections (longer duration of treatment at higher doses):

Headache has been reported very commonly (≥10%).

Reversible alopecia (thinning of hair, and moderate hair loss) and fever have been reported commonly (≥1% and <10%).

Hepatitis has been uncommonly associated with albendazole treatment.

Blood disorders such as pancytopenia, aplastic anaemia and agranulocytosis have been associated very rarely with albendazole treatment. Patients with liver disease, including hepatic echinococcosis, appear to be more susceptible to bone marrow suppression (see Precautions).

There have been very rare cases of Erythema multiforme and Stevens-Johnson syndrome.

DOSAGE AND ADMINISTRATION

ZENTEL 200mg chewable tablets may be crushed, chewed, or swallowed whole.

Adults and Children (over two years):

- *Enterobius vermicularis*, *Ascaris lumbricoides*, *Ancylostoma duodenale, Necator americanus* and *Trichuris trichiura*: 400mg (two ZENTEL 200mg tablets) as a single dose, taken on an empty stomach.

- Suspected or confirmed *Strongyloides stercoralis* infestation: ZENTEL 400mg once daily, taken on an empty stomach for three consecutive days. Patients should then be appropriately followed for at least 2 weeks to confirm cure.

- Cutaneous *larva migrans*: 400mg once daily, taken with food for one to three days has been reported to be effective.

- Suspected or confirmed *Taenia* spp. or *Hymenolepis nana* infestation, when other susceptible helminths species are present: ZENTEL 400mg once daily, taken on an empty stomach for three consecutive days. If the patient is not cured after three weeks, a second course of ZENTEL treatment is indicated. In cases of proven *H. nana* infestation, retreatment in 10-21 days is recommended. (see WARNINGS AND PRECAUTIONS)

- Mixed worm infestations including *Opisthorchis viverrini* and *Clonorchis sinensis*: 400mg twice a day, taken with food for three days is effective. Patients should be re-examined 1 month after treatment to confirm fluke eradication.

OVERDOSAGE

Further management should be as clinically indicated or contact the Poisons Information Centre (telephone 131126) for advice on overdose management.

STORAGE

ZENTEL tablets should be stored below 30°C.

PRESENTATION

ZENTEL - chewable tablets containing 200mg albendazole white to off-white, circular, biconvex, bevel edged film coated tablet, with a pentagonal pyramid on each face, blisters or bottles of 6 tablets.

NAME AND ADDRESS OF SPONSOR:

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Version 3.0
Date of TGA Approval: 25 January 2011