PRODUCT INFORMATION

ESKAZOLE ® TABLETS

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

CAS REGISTRY NUMBER: 54965-21-8

DESCRIPTION
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
ESKAZOLE (albendazole) is effective in the long term treatment of tissue helminth infections, including hydatid disease (echinococcosis), caused by infestation with the tapeworm, Echinococcus granulosus. ESKAZOLE is also effective in the treatment of larval Taenia solium infection (cysticercosis), particularly where there is neurological involvement (neurocysticercosis) (see INDICATIONS).

Albendazole therapy has also been used in the short term treatment of a wide range of intestinal helminth infections.

The anthelmintic action of albendazole is thought to be mainly intra-intestinal. However at the higher doses recommended for ESKAZOLE, sufficient amounts of albendazole are absorbed and metabolised to the active sulphoxide metabolite, to have a therapeutic effect against tissue parasites including hydatid cysts and cysticerci.

Albendazole exhibits larvicidal, ovicidal and vermicide activity, and is thought to exert its anthelmintic effect by inhibiting tubulin polymerization. This causes a cascade of metabolism disruption, including energy depletion, which immobilises 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 due to the low aqueous solubility of albendazole.

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.

There is wide inter-subject variability in plasma sulphoxide concentrations, which is believed related to differences in absorption rather than differences in metabolism. Following oral administration of a single dose of 400mg albendazole in fasting patients, the maximum plasma concentration of albendazole sulphoxide occurred approximately 2½ hours after dosing and ranged from 0.4 to 1.6 μmol/L. In patients taking albendazole with breakfast (estimated fat content 40g) the maximum plasma concentration of albendazole sulphoxide ranged from 1.8 to 6.0 μmol/L after approximately 3¾ hours. The corresponding area under the curve (AUC) values also increased when albendazole was taken with breakfast, from a median of 4.1 to 20.6 μmol/L.h over the first 8 hours. Large inter-subject variability in AUC values for both the fasting or fed states has been reported. The systemic pharmacological effect of albendazole is therefore augmented if the dose is administered with a fatty meal, which significantly enhances absorption (approximately 5 fold).

Albendazole sulphoxide and its metabolites appear to be principally eliminated in bile, with only a small proportion appearing in the urine. Elimination from cysts (and possibly from host tissues) has been shown to occur over several weeks following high and prolonged dosing, so that low levels of albendazole sulphoxide may occur in plasma for several weeks.

INDICATIONS

Hydatid Disease
The long term use of ESKAZOLE is indicated for the treatment of hydatid cysts caused by *E. granulosus* in adults and children over 6 years of age, where surgical intervention is not feasible because of anatomic site or the presence of multiple cysts. Albendazole shows greatest efficacy in the treatment of liver, lung and peritoneal cysts. Experience with bone cysts or those in the heart or central nervous system is limited, but cases of successful treatment with a prolonged course of albendazole have been reported.

ESKAZOLE may also be used as an adjunct to surgical excision of hydatid cysts either:

1) prior to surgical intervention, or

2) post-operatively, if pre-operative treatment was too short (less than two separate 28-day cycles) or if viable cysts are found at surgery.

Larval Taeniasis (Neurocysticercosis)
ESKAZOLE is effective in the treatment of neurocysticercosis (NCC) in courses as short as 7 days.

Other Indications
There is also evidence that ESKAZOLE is effective against *Capillaria philippinensis* in courses of 10 days.

CONTRAINDICATIONS

ESKAZOLE should not be administered during pregnancy or in women thought to be pregnant. ESKAZOLE 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 ESKAZOLE (see Use in Pregnancy, Category D).

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

There is limited experience of use of ESKAZOLE in children under six years of age, therefore use in this age group is not recommended.
PRECAUTIONS

In clinical trials involving patients with hydatid disease, approximately 16% of subjects experienced mild to moderate elevations of liver enzymes during the treatment cycle. Rare severe cases were associated with histological hepatocellular damage, which may be irreversible, and jaundice. Enzyme abnormalities have usually normalised on discontinuation of treatment. In patients with hydatid disease, liver function tests should be obtained before the start of each treatment cycle and at least every two weeks during treatment. Patients with disturbed liver function tests prior to commencing albendazole therapy should be carefully evaluated, since the drug is metabolised by the liver and has been associated with idiosyncratic hepatotoxicity. In patients with hepatic hydatidosis, it should be determined whether the underlying disease or another process is affecting liver function. If enzymes are significantly increased (greater than twice the upper limit of normal) during treatment, ESKAZOLE should be discontinued. ESKAZOLE treatment may be reinstated when levels have returned to normal limits, but liver function should be monitored frequently during repeat therapy.

ESKAZOLE has been occasionally associated with reversible modest reductions in total white cell counts in patients with hydatid disease. In hydatid disease patients blood counts should be performed at the start and every two weeks during each 28 day treatment cycle. ESKAZOLE may be continued if the decrease appears modest and does not progress.

In patients treated with ESKAZOLE for hydatid disease, appropriate long term monitoring should be considered, since approximately 14% of patients followed for 2 years developed recurrent cysts.

The therapeutic action of albendazole in the treatment of neurocysticercosis, may exacerbate presenting symptoms or precipitate new neurological disturbances (e.g. headache, nausea, convulsions, visual changes). These symptoms should be anticipated and patients treated accordingly. (see ADVERSE EFFECTS)

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 taeniosis 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.

Use in Impaired Renal function
The use of ESKAZOLE in patients with impaired renal function has not been studied.

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. ESKAZOLE is contraindicated during pregnancy, and for one month prior to conception. In order to avoid administering albendazole during early pregnancy, women of childbearing age should initiate treatment only after a negative pregnancy test. These tests should be repeated before initiating the next cycle. Women of childbearing age should be advised to take effective precautions against conception during and within one month of completion of treatment with albendazole for a systemic infection.

The use of ESKAZOLE 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 effects of albendazole on the human foetus.

Use in lactation

It is not known if ESKAZOLE or its metabolites are secreted in human breast milk. Therefore breast feeding should be discontinued during and for at least one month after treatment.

Interactions

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

ADVERSE EFFECTS

In clinical trials, ESKAZOLE was associated with new adverse events in approximately 15% of patients treated for hydatid disease. Drug related withdrawals were predominantly due to either hepatic abnormalities (3.8%) or leucopenia (0.7%).

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

More common (≥1%)

In approximately 16% of patients, ESKAZOLE treatment has been associated with mild to moderate elevations of liver enzymes, which have normalised on discontinuation of treatment. (see PRECAUTIONS).

Gastrointestinal disturbances (abdominal pain, nausea, vomiting), dizziness and headache have been reported at incidences of 1-3%. These events are often likely to be associated with the underlying hydatid disease.

Leucopenia has been reported in approximately 2% of hydatid patients during ESKAZOLE treatment cycles.

A high proportion of patients treated for neurocysticercosis experienced adverse events. Neurological events, headache and hyperpyrexia are considered to be related to the therapeutic effect of albendazole. (see PRECAUTIONS)

As with other benzimidazole, reversible alopecia (thinning of hair, and moderate hair loss) hypersensitivity reactions including pruritus, urticaria and rash have been reported. Fever has been reported during the first few days of treatment.

Rare (< 0.1%)

There have been rare reports of pancytopenia and thrombocytopenia.
There have been rare reports of severe hepatic abnormalities, which were associated with histological hepatocellular damage which may be irreversible, and jaundice.

In the treatment of hydatid disease, events reported in individual patients included pancreatitis and ocular maculopathy.

**DOSAGE AND ADMINISTRATION**

**ESKAZOLE 400mg chewable tablets** may be crushed, chewed, or swallowed whole.

To increase the systemic bioavailability of albendazole in the treatment of tissue helminth infections, ESKAZOLE tablets should be taken with a meal. (see PHARMACOLOGY)

**HYDATID DISEASE** (Echinococcosis)

**Adults:**
ESKAZOLE is administered orally at a total daily dose of 800 mg, given in divided doses of 400 mg twice daily, taken with meals, for a total of 28 days. This 28-day treatment period may be repeated after a 14-day drug free period for a total of three cycles.

For patients weighing less than 60 kg the dose is 15mg/kg/day in divided doses according to the dosage schedule listed above.

**Children (six years and over):**
There has been no experience to date with the use of ESKAZOLE in hydatid disease in children under six years of age, therefore, usage for this indication in children younger than six years is not recommended. (See CONTRAINDICATIONS).

The recommended dose for children 6 years of age and over is 15mg/kg/day given in divided doses according to the dosage schedule listed above.

- **Inoperable and Multiple Cysts:**
  Up to three 28-day cycles of ESKAZOLE treatment may be given. If there is no evidence of treatment efficacy (shrinkage or disappearance of cyst(s), alteration in X-ray appearance or ultrasound/CT scan density or membrane separation) in sites such as liver, lung or peritoneum within three cycles, further treatment is unlikely to produce a response. More prolonged treatment may be required for sites such as bone or brain.

- **Preoperatively:**
  Two 28-day cycles should be given prior to surgery. Where surgical intervention is necessary before completion of two cycles, ESKAZOLE should be given for as long as possible, but for not more than 28 days per cycle.

- **Peri and Post Surgery:**
  Where only a short pre-operative course has been given (less than 14 days), and in cases where emergency surgery is required, ESKAZOLE should be given post-operatively for two 28-day cycles separated by 14 drug free days. Additionally where cysts are found to be viable following pre-surgical treatment, a full two cycle course should be given.

**LARVAL TAENIASIS** (Neurocysticercosis)

**Adults:**
The dose is 800mg daily, taken in two divided doses (400 mg twice daily) with meals for a minimum of 7 days, dependant on response. In limited studies, a course of 3 days has also been found to be adequate.

For patients weighing less than 60 kg the dose is 15mg/kg/day given in divided doses according to the dosage schedule listed above.
Appropriate steroid, antihistamine and/or anticonvulsant therapy should be administered as required. Oral or intravenous corticosteroids are recommended to prevent cerebral hypertensive episodes during the first week of treatment.

There is information suggesting individuals not responding to one course may benefit from a second course, and that the second course may result in cure. A two-week drug-free interval should be maintained between courses.

**Children (six years and over):**
There has been no experience to date with the use of ESKAZOLE in children under six years of age, therefore usage is not recommended. (See CONTRAINDICATIONS)

The recommended dose for children 6 years of age and over is 15mg/kg/day given in divided doses according to the dosage schedule listed above.

**CAPILLARIA PHILIPPINENSIS**
In adults, one tablet (400mg) daily for 10 days is reported to be effective.

**OVERDOSAGE**
There is no experience of overdosage. No specific antidote is known. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

**PRESENTATION AND STORAGE CONDITIONS**
ESKAZOLE tablets should be stored below 30°C. Under these conditions the shelf life of the tablets is 5 years.

ESKAZOLE - Tablets containing 400 mg albendazole: chewable, mottled, pale orange, rounded oblong, biconvex, tablets with a score line on one side and engraved ALB 400 on the other, in blister packs of 56* and in bottles of 60 tablets. ESKAZOLE tablets have a distinctive fruity odour.

Eskazole tablets also contain the following ingredients: lactose, microcrystalline cellulose, maize starch, croscarmellose sodium, Povidone K30, sodium lauryl sulfate, sunset yellow CI 15985, sodium saccharin, magnesium stearate, vanilla flavour, passion fruit flavour and orange flavour.

* Not currently available.

**NAME AND ADDRESS OF THE SPONSOR**
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**POISON SCHEDULE OF THE MEDICINE: S4**
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