The Content of this leaflet was approved by the Ministry of Health in May 2017 and updated according to the guidelines of the Ministry of Health in May 2018

Eskazole

1. NAME OF THE MEDICINAL PRODUCT

Eskazole

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of albendazole as active substance.

Excipients with known effect
It contains lactose and sunset yellow lake E110.
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For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

4. CLINICAL PARTICULARS

Albendazole is a benzimidazole carbamate with antihelmintic and antiprotozoal activity against intestinal and tissue parasites.

4.1. Therapeutic indications

Albendazole is indicated for the treatment of the following systemic helminth diseases (see section 5.1 for details about susceptible helminth species):

- **Echinococcosis (hydatid disease)**

Albendazole is indicated for the treatment of liver, lung and peritoneal cysts. Experience with bone cysts and those in the central nervous system and heart is limited.

Cystic echinococcosis (caused by *Echinococcus granulosus*)
Albendazole is used in patients with cystic echinococcosis:

1. When surgical intervention is not feasible.
2. As a co-adjunct to surgical treatment.
3. Prior to surgical intervention.
4. If preoperative treatment was too short, if spillage has occurred or if viable cysts were found at surgery.
5. Following percutaneous drainage of cysts for diagnostic or therapeutic reasons.

Alveolar echinococcosis (caused by *Echinococcus multilocularis*)

Although its efficacy has not been completely demonstrated in clinical trials, albendazole is used in patients with alveolar echinococcosis in the following situations:

1. In inoperable disease, particularly in cases of local or distant metastasis.
2. Following palliative surgery.
3. Following radical surgery or liver transplantation.

4.2. Posology and method of administration

Posology
There is limited experience of use of albendazole in children under 6 years of age; therefore use in children under this age is not recommended.

Dosages are dependent on the parasites involved, the weight of the patient, and the seriousness of the infection.

- **Cystic Echinococcosis**

Patients weighing > 60 kg: Total daily dose of 800 mg, given in two divided doses of 400 mg for a total of 28 days.

Patients weighing < 60 kg: Total daily dose of 15 mg/kg given in two equally divided doses (maximum dose of 800 mg/day) for a total of 28 days.

These 28-day cycles of treatment may be repeated after a 14-day period without treatment between cycles depending on the therapeutic indication, for a total of 3 cycles.

1. Inoperable and multiple cysts
Up to three 28-day cycles of treatment with albendazole may be given for the treatment of liver, lung and peritoneal cysts. More prolonged treatment may be required for bone and brain locations.

2. Preoperative
Two 28-day cycles should be given prior to surgery. Where surgical intervention is necessary before completion of two cycles, albendazole should be given for as long as possible.

3. Postoperative
Where only a short preoperative course has been given (less than 14 days) and in those cases where emergency surgery is required, albendazole should be given postoperatively for two 28-day cycles separated by a 14-day period without treatment.
Additionally, if cysts are viable following presurgical treatment or if spillage has occurred, a full two-cycle course should be given.

4. After percutaneous cyst drainage
Similar treatment as for postoperative.

- **Alveolar echinococcosis**

Patients weighing > 60 kg: Total daily dose of 800 mg, given in two divided doses of 400 mg for 28-day cycles with 14-day periods without treatment between cycles.

Patients weighing < 60 kg: Total daily dose of 15 mg/kg given in two equally divided doses (maximum dose of 800 mg/day) for 28-day cycles with 14-day periods without treatment between cycles.

Treatment is given in 28-day cycles. It may be prolonged for months or even years.

Continuous treatment at the same dose has been used for periods of up to 20 months.

Current follow up suggests that survival times are substantially improved after prolonged treatment. It has been demonstrated in a limited number of patients that continuous treatment may lead to an apparent cure.

- Elderly

Experience in patients 65 years of age or older is limited. Reports indicate that no dose adjustment is required; however, albendazole should be used with caution in elderly patients with evidence of hepatic dysfunction (see section 4.2 “Hepatic impairment” and section 5.2).

- Renal impairment

Since renal excretion of albendazole and its primary metabolite, albendazole sulfoxide, is negligible, it is unlikely that clearance of these compounds would be altered in these patients. No dose adjustment is required; however, patients with evidence of renal impairment should be carefully monitored.

- Hepatic impairment

Since albendazole is rapidly metabolized by the liver to its primary pharmacologically active metabolite, albendazole sulfoxide, hepatic impairment would be expected to have significant effects on the pharmacokinetics of albendazole sulfoxide. Patients with abnormal hepatic function test results (transaminases) prior to starting treatment with albendazole should be carefully evaluated and treatment should be discontinued if hepatic enzymes are significantly increased or full blood count decreases to a clinically significant level (see sections 4.4 and 4.8).

Method of administration

Eskazole should be taken with meals (see section 5.2).

Some people, particularly young children, may experience difficulties swallowing the tablets whole and should be encouraged to chew them with a little water or alternatively, they may be crushed.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Albendazole should not be administered during pregnancy or in women thought to be pregnant.

In order to avoid administering albendazole during the first months of pregnancy, women of child-bearing age should initiate treatment only after a negative pregnancy test. This test should be repeated at least once before initiating the next cycle. Moreover, women of child-bearing age are advised to take effective contraceptive measures during treatment and for one month after completion.

4.4. Special warnings and precautions for use

Treatment with albendazole has been associated with mild to moderate elevations of hepatic enzymes. Hepatic enzymes generally normalized after treatment discontinuation. Cases of hepatitis have been reported (see section 4.8). Therefore, hepatic function tests should be obtained before the start of each treatment cycle, and at least every two weeks during treatment. If hepatic enzymes are significantly increased (greater than twice the upper limit of normal), treatment should be discontinued. Treatment may be restarted when hepatic enzymes have returned to normal limits, but patients should be carefully monitored for recurrence.

Patients with abnormal hepatic function test results prior to initiating treatment should be closely monitored due to the hepatotoxic potential of albendazole.

Albendazole has been shown to cause bone marrow suppression and therefore, blood counts should be performed at the start of treatment and every two weeks during each 28-day cycle. Patients with hepatic disease, including hepatic echinococcosis, appear to be more susceptible to bone marrow suppression leading to pancytopenia, aplastic anemia, agranulocytosis and leukopenia, and therefore warrant closer monitoring of blood counts. Treatment with albendazole should be discontinued if clinically significant decreases in blood cell counts occur (see sections 4.2 and 4.8).

In order to avoid administering albendazole during early pregnancy, women of child-bearing age should:

- initiate treatment only after a negative pregnancy test. These tests should be repeated at least once before initiating the next cycle.

- be advised to take effective contraceptive measures during and for one month after completion of treatment with albendazole for a systemic infection.

Pre-existing neurocysticercosis may also be detected in patients treated with albendazole for other conditions, particularly in areas with high taenosis infection. Patients may experience neurological symptoms such as 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, and the appropriate treatment with anticonvulsant drugs and steroids should be started immediately.

In rare cases of retinal neurocysticercosis, the patient should be examined for retinal lesions before beginning treatment. If these lesions are observed, the benefit of the therapy should be weighed against the possibility of retinal damage.

Warnings for excipients
This medicinal product contains lactose. Patients with hereditary galactose intolerance, the Lapp lactase deficiency (deficiency observed in certain populations of Laponia) or glucose-galactose malabsorption should not take this medicine.

This medicinal product may cause allergic reactions because it contains
sunset yellow lake E110 colorant.

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

It has been observed that cimetidine, praziquantel and dexamethasone increase the plasma levels of the albendazole active metabolite.

Ritonavir, phenytoin, carbamazepine and phenobarbital may reduce plasma concentrations of the albendazole active metabolite, 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 regimens or treatments.

4.6. Fertility, pregnancy and lactation

Pregnancy
Eskazole should not be administered during pregnancy or in women thought to be pregnant (see section 4.3).

Breast-feeding
There are no available data about its use during breastfeeding in humans or animals. Therefore, Eskazole should not be used during breast-feeding.

4.7. Effects on ability to drive and operate machinery

Studies to determine the effect of Eskazole on the ability to drive and operate machinery have not been conducted. However, it should be taken into account that dizziness has been reported after using albendazole (see section 4.8).

4.8. Undesirable effects

Data from large clinical studies were used to determine the frequency of adverse reactions classified as very common to rare. The frequencies assigned to all other reactions (i.e. those occurring in < 1/1000) were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency.

The following convention (or agreement) has been used for the classification of frequency:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10,000 and < 1/1000
Very rare	< 1/10,000

Use in systemic helminth infections:

Blood and lymphatic system disorders
Uncommon: leukopenia
Very rare: pancytopenia, aplastic anemia, agranulocytosis

Leukopenia has been associated with albendazole when treating patients with echinococcosis.

Patients with hepatic disease, including hepatic echinococcosis, appear to be more susceptible to bone marrow suppression (see sections 4.2 and 4.8).

Immune system disorders
Uncommon: hypersensitivity reactions including rash, pruritus and urticaria

Nervous system disorders
Very common: headache
Common: dizziness

Gastrointestinal disorders
Common: gastrointestinal disturbances (abdominal pain, nausea, vomiting)

Gastrointestinal disturbances have been associated with albendazole when treating patients with echinococcosis.

Hepatobiliary disorders
Very common: mild to moderate elevation of hepatic enzymes.
Uncommon: hepatitis

Skin and subcutaneous tissue disorders
Common: reversible alopecia (thinning of hair and moderate hair loss)
Very rare: erythema multiforme, Stevens-Johnson syndrome

General disorders and administration site conditions
Common: fever

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il
Additionally, you should also report to GSK Israel (il.safety@gsk.com**).**

4.9. Overdose

Treatment for overdose should be adjusted as clinically indicated or as recommended by the National Poisons Centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: benzimidazole derivatives, ATC code: P02CA03

Albendazole is a benzimidazole carbamate with antihelmintic and antiprotozoal effect against tissue and intestinal parasites. Albendazole exhibits larvicidal, ovicidal and vermicidal activity, and it is thought to exert its antihelmintic effect by inhibiting tubulin polymerization. This causes the disruption of the helminth metabolism, including energy depletion, which immobilizes and then kills the susceptible helminth.

Albendazole is effective in the treatment of tissue parasites including cystic echinococcosis and alveolar echinococcosis caused by infestation of *Echinococcus granulosus* and *Echinococcus multilocularis*, respectively.

Albendazole has been shown (in clinical trials) to eradicate cysts or significantly reduce cyst size in up to 80% of patients with cysts caused by *Echinococcus granulosus.*

Where cysts have been investigated for viability following treatment with albendazole, 90% have been non-viable in laboratory or animal studies compared to only 10% of untreated cysts.

Clinical experience with albendazole shows that during treatment of cysts due to *Echinococcus multilocularis* with albendazole, a minority of patients were considered cured and a majority had an improvement or stabilization of disease.

5.2. Pharmacokinetic properties

Absorption
In man, albendazole is poorly absorbed (<5%) following oral administration.
Albendazole rapidly undergoes first-pass metabolism in the liver, and is generally not detected in plasma.
Albendazole sulfoxide is the primary metabolite, which is thought to be the active moiety in effectiveness against systemic tissue infections. The plasma half-life of albendazole sulfoxide is 8.5 hours.
It has been reported that following oral administration of a single dose of 400 mg albendazole taken with breakfast, the pharmacologically active metabolite, albendazole sulfoxide, achieves plasma concentrations from 1.6 to 6.0 μmol/L.
The systemic pharmacological effect of albendazole is augmented if the dose is administered with a fatty meal, which enhances the absorption by approximately 5-fold.

Excretion
Albendazole and its metabolites appear to be principally excreted in bile, with only a small proportion appearing in urine. Excretion from cysts has been shown to occur after several weeks of prolonged treatment.

Special patient populations

- Elderly

Although no studies have investigated the effect of age on albendazole sulfoxide pharmacokinetics, results in twenty-six patients with hydatid cyst (up to 79 years) suggest pharmacokinetics similar to those in young subjects. The number of elderly patients treated for either hydatid disease is limited, but no problems associated with an older population are observed.

- Patients with renal impairment

The pharmacokinetics of albendazole in patients with impaired renal function have not been studied.

- Patients with hepatic impairment

The pharmacokinetics of albendazole in patients with impaired hepatic function have not been studied.

5.3. Preclinical safety data

Albendazole has been shown to be teratogenic and embryotoxic in rats and rabbits. It was negative for evidence of mutagenicity or genotoxicity in a panel of *in vitro* (including Ames activated and inactivated) and *in vivo* tests. In long term toxicity studies conducted in rats and mice at daily doses of up to 30 times the recommended human doses, no treatment-related tumor formation was observed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose E460, maize starch, lactose, croscarmellose sodium, povidone, orange flavor, vanilla flavor, magnesium stearate, sodium lauryl sulfate, passion fruit flavor, sodium saccharin, sunset yellow lake E110.

6.2. Incompatibilities

None reported.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

Store below 25°C.

6.5. Nature and contents of container

'Securitainer' containing 60 tablets or blisters containing 12, 56 or 100 tablets.

6.6. Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

GlaxoSmithKline Consumer Healthcare South Africa (PTY) Limited, Cape Town, South Africa.

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

9. LICENSE NUMBER

114-55-27464

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