SUMMARY PRODUCT CHARACTERISTIC (SPC)

ALBENDAZOLE
400, chewable tablets

1. NAME OF THE MEDICAL PRODUCT - ALBENDAZOLE
1.2 INTERNATIONAL NON-PROPERTY NAME – ALBENDAZOLE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains:
active ingredient: Albendazole – 400.0 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.
A pink, round, mottled, tablet with beveled edges and with raspberry odor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Albendazole is a benzimidazole carbamate anthelmintic for use in the treatment caused by intestinal and tissue parasites: Roundworm (Ascaris lumbricoides), pinworm (Enterobius vermicularis), hookworm (Necator americanus, Ancylostoma duodenale), whipworm (Trichuris trichiura), threadworm (Strongyloides stercoralis), tapeworm (Taenia spp and Hymenolepis nana only in the case of associated parasitism), Chlonorchiasis (Chlonorchis sinensis), Opisthorchiasis (Opisthorchis viverrini) and cutaneous larva migrans; Giardiasis (G.lamblia, G.duodenalis, G.intestinalis, Lamblia intestinalis) in children, Cystic Echinococcosis (caused by *Echinococcus granulosus*), Alveolar Echinococcosis (caused by *Echinococcus multilocularis*), Neurocysticercosis (caused by infection with *Taenia solium*, a tapeworm), Hepatic capillariasis, caused by *Capillaria hepatica, Gnathostomiasis (also known as larva migrans profundus caused by the nematode (roundworm) Gnathostoma spinigerum and/or Gnathostoma hispidum),* Trichinellosis (caused by roundworms of the genus *Trichinella),* Toxocarosis (caused by Toxocara spp).

4.2 Posology and method of administration

Route of administration: Oral.

Dosage: Dosages are dependent on the parasite involved, the weight of the patient, and the severity of the infection:

Intestinal parasites and cutaneous larva migrans

Indications	Age	Dose	Period
- Roundworm - Pinworm - Hookworms - Whipworm	adults and children over 6 years of age	400 mg	single dose
- Strongyloidiasis	adults and children over 6	400 mg	one dose per

- Taeniasis - Hymenolepiasis	years		day for 3 days In cases of proven Hymenolepiasis, retreatment in 10-21 days is recommended.
-.Chlonorchiasis - Opisthorchiasis	adults and children over 6 years of age	400 mg	two doses per day for 3 days
- Cutaneous larva migrans	adults and children over 6 years of age	400 mg	one dose per day from1 to 3 days
- Giardiasis	children 6 - 12 years of age only	400 mg	one dose per day for 5 days

Systemic helminthic infections (long-term treatment with higher doses)

Cystic Echinococcosis	28 days. In inoperable form three 28-day treatment cycles recommended, separated by a 14-day break in dosing. Before the surgery, it recommended two 28-day cycles, separated by a 14-day break in dosing. If preoperative course of less than 14 days and viable cysts found after surgery it should administer two cycles of 28 days, separated by a 14-day break in taking the drug
Alveolar Echinococcosis	28 days. The second 28-day course is repeated after two week break in taking the drug. Treatment can be continued for months or years.
Neurocysticercosis	Course duration from 7 days to 31 days. The second course may be repeated after a two-week break in taking the drug.
Hepatic capillariasis	400 mg one dose per day for 10 days
Gnathostomiasis	400 mg one dose per day for 10-20 days
Trichinellosis and Toxocarosis	400 mg two doses per day for 5-10 days

Treatment may need to be prolonged for months or years. Continuous treatment at the same dose has been used for periods of up to 20 months.

Method of administration

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

Cystic Echinococcosis

1. Inoperable and multiple cysts

Up to three 28-day cycles of albendazole may be given for the treatment of liver, lung and peritoneal cysts. More prolonged treatment may be required for sites such as bone and brain.

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

3. Post-operative
Where only a short pre-operative course has been given (less than 14 days) and in cases where emergency surgery is required, albendazole 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 or where spillage has occurred, a full two-cycle course should be given.
4. After percutaneous cyst drainage. Treatment as for post-surgery above.

Alveolar Echinococcosis
Treatment is normally given in 28 day cycles as for cystic echinococcosis. It may have to be continued for months or even years. Current follow up suggests that survival times are substantially improved following prolonged treatment. Continuous treatment has been shown in a limited number of patients to lead to apparent cure.

Special Populations

Children
There has been limited experience to date with the use of albendazole in children under six years of age; therefore, usage in children less than six years is not recommended. The recommended dose for older children is 12 mg/kg body weight/day in divided doses.

Elderly
Experience in patients 65 years of age or older is limited. Reports indicate that no dosage adjustment is required; however, albendazole should be used with caution in elderly patients with evidence of hepatic dysfunction (see 'Hepatic impairment' below and '5.2 Pharmacokinetic Properties').

Renal impairment
Since renal elimination 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 dosage adjustment is required; however, patients with evidence of renal impairment should be carefully monitored.

Hepatic impairment
Since Albendazole is rapidly metabolised by the liver to the primary pharmacologically active metabolite, albendazole sulfoxide, hepatic impairment would be expected to have significant effects on the pharmacokinetics of albendazole sulfoxide. 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 or full blood count decreased by a clinically significant level (see '4.4 Special Warnings and Precautions for Use' and '4.8 Undesirable Effects').

4.3 Contraindications

Albendazole should not be administered during pregnancy or in women thought to be pregnant. Women of childbearing age should be advised to take effective precautions, with non hormonal contraceptive measures, against conception during and within one month of completion of treatment with Albendazole.
Albendazole is contra-indicated in patients with a known history of hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
Albendazole has been associated with mild to moderate elevations of hepatic enzymes. Hepatic enzymes generally normalise on discontinuation of treatment. Case reports of hepatitis have also been received (see '4.8 Undesirable Effects'). Liver 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), albendazole should be discontinued. Treatment may be restarted when hepatic enzymes have returned to normal limits, but patients should be monitored for recurrence.

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 leucopenia and therefore warrant closer monitoring of blood counts.
Albendazole should be discontinued if clinically significant decreases in blood cell counts occur (see '4.2 Posology and Method of Administration' and '4.8 Undesirable Effects').

Precautions:
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 at least once before initiating the next cycle.
- be advised to take effective precautions against conception during and within one month of completion of treatment with albendazole for a systemic infection.

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Albendazole has been shown to induce liver enzymes of the cytochrome P450 system responsible for its own metabolism.

Drugs that can reduce the effectiveness of albendazole – monitor effect – other dose regimens or therapies may be required.

- Anticonvulsants (eg phenytoin: fosphenytoin: carbamazepine: phenobarbital: primidone)
- Levamisole
- Ritonavir

Drugs that may increase levels of the active metabolite of albendazole – monitor to possible increased albendazole adverse effects.

- Cimetidine
- Dexamethasone (continuous use raises albendazole levels by 50%)
- Praziquantel

Grapefruit juice also increases the plasma levels of albendazole sulfoxide.
Other possible interactions
Because of possible alterations in cytochrome P450 activity, there is a theoretical risk of an interaction with the following

- Oral contraceptives
- Anticoagulants
- Oral hypoglycaemics
- Theophylline

Care should be exercised when albendazole is given to patients taking these medicines.

4.6 Fertility, pregnancy and lactation
Pregnancy:
Albendazole should not be administered during pregnancy or in women thought to be pregnant (see contraindications).

Breast-feeding:
It is not known whether albendazole or its metabolites are secreted in human breast milk. Thus Albendazole should not be used during lactation unless the potential benefits are considered to outweigh the potential risks associated with treatment.

4.7 Effects on ability to drive and use machines
Dizziness is reported as a common reaction. Patients should be advised that if affected they should not drive, operate machinery or take part in activities where this could put them or others at risk.

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

The following convention has been used for the classification of frequency:

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

Blood and the lymphatic system disorders
Uncommon: Leucopenia
Very rare: Pancytopenia, aplastic anaemia, agranulocytosis

Patients with liver disease, including hepatic echinococcosis, appear to be more susceptible to bone marrow suppression (see '4.2 Posology and Method of Administration' and '4.4 Special Warnings and Precautions for Use').

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.

Hepato-biliary disorders
Very common: Mild to moderate elevations 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 administrative 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. Healthcare professionals are asked to report any suspected adverse reactions via the "Report about adverse effect of medicine" at: www.pharm.am.

4.9 Overdose
In case of overdosage, symptomatic therapy (gastric lavage) and general supportive measures should be undertaken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anthelmintic
ATC code: P02CA03

Albendazole is a benzimidazole carbamate with anthelmintic effects against tissue parasites. Albendazole exhibits larvicidal, ovicidal and vermicidal activity, and it is thought to exert its anthelmintic effect by inhibiting tubulin polymerisation. This causes the disruption of the helminth metabolism, including energy depletion, which immobilises 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.

In the treatment of cysts due to *E. multilocularis*, a minority of patients were considered to be cured and a majority had an improvement or stabilisation of disease due to albendazole.

5.2 Pharmacokinetic properties

Absorption and metabolism

In man, albendazole is poorly absorbed (<5%) following oral administration. Albendazole rapidly undergoes extensive 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 8½ hours.

Following oral administration of a single dose of 400 mg albendazole, the pharmacologically active metabolite, albendazole sulfoxide, has been reported to achieve plasma concentrations from 1.6 to 6.0 micromol/litre when taken with breakfast. 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 sulfoxide and its metabolites appear to be principally eliminated in bile, with only a small proportion appearing in the urine. Elimination from cysts has been shown to occur over several weeks following high and prolonged dosing.

Special Patient Populations

Elderly

Although no studies have investigated the effect of age on albendazole sulfoxide pharmacokinetics, data in 26 hydatid cyst patients (up to 79 years) suggest pharmacokinetics similar to those in young healthy subjects. The number of elderly patients treated for either hydatid disease or neurocysticercosis is limited, but no problems associated with an older population have been observed.

Renal Impairment

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

Hepatic Impairment

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

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Microcrystalline cellulose
Povidone
Magnesium stearate
Sodium starch glycolate
Maize starch
Sodium lauryl sulphate
Color red E-129
Sodium saccharin
Sodium carboxymethylcellulose
Raspberry flavor

6.2 Incompatibilities
None known

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store at temperature not higher than 25^0C, in a dry place, and protect from light.
Keep out of the reach of children.

6.5 Nature and contents of container
4 tablets in a plastic bottle with leaflet in the cardboard box.

6.6 Special precautions for disposal and other handling
None

7. MANUFACTURER
"ARPIMED" LLC
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8. MARKETING AUTHORIZATION HOLDER
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