For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

ZENTEL

1. GENERIC NAME

Albendazole Tablets IP / Albendazole Oral Suspension IP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablet

Each uncoated chewable tablet contains:
Albendazole IP 400 mg
Colour: Sunset Yellow FCF.
Excipients q.s.

Suspension

Each 10 ml contains:
Albendazole IP 400 mg in a flavoured syrup base.

List of Excipients

Tablets

Lactose, Starch, Polyvinylpyrrolidone, Sodium Lauryl Sulphate, Saccharin Sodium, Sunset Yellow FCF, Microcrystalline Cellulose, Sodium Starch Glycolate (Type A), Trusil Vanilla Special, Trusil Orange Special, Magnesium Stearate, Purified water.

Suspension

Polysorbate 80, Glycerin, Sorbitol Solution 70%, Methylparaben, Propylparaben, Sodium carboxymethyl cellulose, Sodium saccharin, American Ice cream flavour, Cardamom flavour, Purified water, Citric Acid Monohydrate.

3. DOSAGE FORM AND STRENGTH

Uncoated Chewable Tablet
Suspension

For information on strength(s) refer *2. Qualitative and Quantitative Composition* above.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

ZENTEL is a benzimidazole carbamate with anthelmintic and antiprotozoal activity against intestinal and tissue parasites.

Intestinal Infections And Cutaneous Larva Migrans

Short duration treatment at low dose.

ZENTEL is indicated in the treatment of the following clinical conditions caused by sensitive intestinal helminths/protozoa (see *5.2 Pharmacodynamic Properties):*

- enterobiasis (pinworm infection)
- ancylostomiasis and necatoriasis (hookworm disease)
- hymenolepsiasis (dwarf tapeworm infection)
- taeniasis (pork/beef tapeworm infection)
- strongyloidiasis (threadworm infection)
- ascariasis (roundworm infection)
- trichuriasis (whipworm infection)
- clonorchiasis and opisthorchiasis (*Opisthorchic viverrini* and/or *Clonorchis sinensis* infections) (liver fluke infections)
- cutaneous larva migrans [hookworm (animal origin) causing skin disease]
- giardiasis in children (*Giardia* infection)

SYSTEMIC HELMINTH INFECTIONS

Longer durations of treatment at higher doses.

ZENTEL is indicated for the treatment of the following systemic helminth infections (see *5.2 Pharmacodynamic Properties*).

Echinococcosis

ZENTEL shows greatest efficacy in the treatment of liver, lung and peritoneal cysts. Experience with bone cysts and those in the heart and central nervous system is limited.

<u>*Cystic Echinococcosis*</u> (caused by *Echinococcus granulosus*)

ZENTEL is used in patients with cystic echinococcosis:

1. where surgical intervention is not feasible.
2. prior to surgical intervention.
3. post-operatively if pre-operative treatment was too short, if spillage has occurred or if viable material was found at surgery.
4. following percutaneous drainage of cysts for diagnostic or therapeutic reasons.

Alveolar Echinococcosis (caused by *Echinococcus multilocularis*)

ZENTEL is used in patients with alveolar echinococcosis:
1. in inoperable disease, particularly in cases of local or distant metastasis.
2. following palliative surgery.
3. following radical surgery or liver transplantation.

Neurocysticercosis (larval *Taenia solium* infection)

ZENTEL is used for the treatment of patients with:
1. single or multiple cystic or granulomatous lesions of the brain parenchyma.
2. arachnoidal or intraventricular cysts.
3. racemose cysts.

4.2 Posology and Method of Administration

Intestinal Infections and Cutaneous Larva Migrans

No special procedures, such as fasting or purging, are required.

If the patient is not cured after three weeks, a second course of treatment is indicated.

Some patients, particularly young children, may experience difficulties swallowing the tablets whole and should be encouraged to chew the tablets with a little water; alternatively the tablets may be crushed. The suspension can also be administered as an alternative.

Infection	**Age**	**Usual Dose**	**Duration of dose**
Enterobiasis (pinworm infection)	Adults and children over 2 years of age.	400 mg	Single dose.
Ancylostomiasis and necatoriasis (hookworm disease) Ascariasis (roundworm infection) Trichuriasis (whipworm infection)	Children 1 to 2 years of age.	200 mg	Single dose.
Suspected or confirmed strongyloidiasis (threadworm infection) Taeniasis (pork/beef tapeworm infection) Hymenolepiasis (dwarf tapeworm infection) †	Adults and children over 2 years of age.	400 mg	Once daily for 3 consecutive days. †In cases of proven hymenolepsiasis, retreatment in 10 to 21 days is recommended.
Chlonorchiasis Opisthorchiasis (liver fluke infections)	Adults and children over 2 years of age.	400 mg	Twice daily for 3 days.

Infection	Age	Usual Dose	Duration of dose
Cutaneous larva migrans [hookworm (animal origin) causing skin disease]	Adults and children over 2 years of age.	400 mg	Once daily for 1 to 3 days.
Giardiasis	Children 2 to 12 years of age only.	400 mg	Once daily for 5 days.

- ***Elderly***

There are limited data on the use of albendazole in patients 65 years of age and over. However, there is no evidence that elderly patients require a different dose than younger adult patients.

- ***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. 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 monitored.

Systemic helminth infections

ZENTEL should be taken with meals (see *5.3 Pharmacokinetic Properties*).

There has been limited experience to date with the use of *ZENTEL* at high doses in children under 6 years of age; therefore use in children less than 6 years is not recommended.

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

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

Infection	Patient Body Weight	Dose	Duration of Dosage
Cystic Echinococcosis	> 60 kg	800 mg given in two divided doses of 400 mg.	Daily for 28 days. Treatment for 28 days may be repeated after a 14 day period without treatment for a total of three cycles.
	< 60 kg	15 mg/kg, given in two equally divided doses (maximum dose 800 mg/day).	
- *Inoperable and multiple cysts*			Up to three 28 day cycles of *ZENTEL* treatment 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.
- *Pre-operative*			Two 28 day cycles should be given where possible prior to surgery. Where surgical intervention is necessary before completion of two cycles, *ZENTEL* should be given for as long as possible.
- *Post-operative* - *After percutaneous cyst drainage*			Where only a short pre-operative course has been given (less than 14 days) and in cases where emergency surgery is required, *ZENTEL* 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.
Alveolar Echinococcosis	> 60 kg	800 mg, given in two equally divided doses.	Daily for 28 days. Treatment for 28 days may be repeated after a 14 day period without treatment. 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.†
	< 60 kg	15 mg/kg given in two equally divided doses (maximum dose 800 mg/day).	
Neurocysticercosis ±	> 60 kg	800 mg, given in two equal divided doses.	Daily for 7 to 30 days, dependent on the response. A second course may be given with a two-week interval between dose regimes.
	< 60 kg	15 mg/kg, given in two equal divided doses (maximum dose 800 mg/day).	

Infection	Patient Body Weight	Dose	Duration of Dosage
- *Parenchymal cysts and granulomas*	> 60 kg	800 mg, given in two equal divided doses.	Treatment is usually continued for a minimum of 7 days up to 28 days.
	< 60 kg	15 mg/kg, given in two equal divided doses (maximum dose 800 mg/day).	
- *Arachnoidal and ventricular cysts*	> 60 kg	800 mg, given in two equal divided doses.	Treatment for 28 days is normally necessary in non-parenchymal cysts.
	< 60 kg	15 mg/kg, given in two equal divided doses (maximum dose 800 mg/day).	
- *Racemose cysts*	> 60 kg	800 mg, given in two equal divided doses.	Treatment is normally required for at least 28 days. This has been given as a continuous treatment, the duration being determined by clinical and radiological response.
	< 60 kg	15 mg/kg, given in two equal divided doses (maximum dose 800 mg/day).	

†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. ±Neurocysticercosis: Patients being treated for neurocysticercosis should receive appropriate steroid and anticonvulsant therapy as required. Oral or intravenous corticosteroids are recommended to prevent cerebral hypertensive episodes during the first week of treatment.

- ***Elderly***

As for 'Intestinal Infections and Cutaneous Larva Migrans'.

- ***Renal impairment***

As for 'Intestinal Infections and Cutaneous Larva Migrans'.

- ***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

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

ZENTEL is contraindicated in patients with a known history of hypersensitivity to albendazole or other constituents of the dose forms.

4.4 Special Warnings and Precautions for Use

Intestinal Infections and Cutaneous Larva Migrans (short duration of treatment at lower doses)

- **Pregnancy**

In order to avoid administering *ZENTEL* during early pregnancy, women of childbearing age should initiate treatment during the first week of menstruation or after a negative pregnancy test.

- **Pre-existing neurocysticercosis**

Treatment with *ZENTEL* may uncover pre-existing neurocysticercosis, particularly in areas with high taenosis (tapeworm) 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. If symptoms occur appropriate steroid and anticonvulsant therapy should be started immediately.

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

- **Influence on hepatic enzymes**

ZENTEL treatment 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), *ZENTEL* should be discontinued. *ZENTEL* treatment may be restarted when hepatic enzymes have returned to normal limits, but patients should be carefully monitored for a recurrence.

- **Bone marrow suppression**

ZENTEL 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. *ZENTEL* 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*).

- **Pregnancy**

In order to avoid administering *ZENTEL* 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 *ZENTEL* for a systemic infection.

- **Neurocysticercosis**

Symptoms associated with an inflammatory reaction following death of the parasite may occur in patients receiving *ZENTEL* 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 *ZENTEL* 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.

Excipients

ZENTEL tablets contain sunset yellow FCF which may cause allergic-type reactions.

4.5 Drug Interactions

Cimetidine, praziquantel and dexamethasone have been reported to increase the plasma levels of the albendazole active metabolite responsible for the systemic efficacy of the product.

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.

4.6 Use in Special Populations

Fertility

There are no data on the effects of albendazole on human fertility.

No effects on male fertility have been observed in animal studies at clinically relevant exposures (see *6. Nonclinical Properties)*

Pregnancy

Albendazole should not be administered during pregnancy or in women thought to be pregnant (see *4.3 Contraindications*).

Lactation

Adequate human or animal data on use during lactation are not available.

4.7 Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *ZENTEL* on driving performance or the ability to operate machinery. However, when driving vehicles or operating machinery, it should be taken into account that dizziness may be expected after using *ZENTEL* (see *4.8 Undesirable Effects*).

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.

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (>1/10), common (>1/100 and <1/10), uncommon (>1/1000 and <1/100), rare (>1/10 000 and <1/1000) and very rare (<1/10 000), including isolated reports.

Intestinal Infections and Cutaneous Larva Migrans (short duration treatment at lower dose)

Immune system disorders

Rare: Hypersensitivity reactions including rash, pruritus and urticaria

Nervous system disorders

Uncommon: Headache and dizziness

Gastrointestinal disorders

Uncommon: Upper gastrointestinal symptoms (e.g. epigastric or abdominal pain, nausea, vomiting) and diarrhoea.

Hepatobiliary disorders

Rare: Elevations of hepatic enzymes

Skin and subcutaneous tissue disorders

Very rare: Erythema multiforme, Stevens-Johnson syndrome

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

Blood and the lymphatic system disorders

Uncommon: Leukopenia
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.

Hepatobiliary 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 administration site conditions

Common: Fever

4.9 Overdose

Symptoms and signs
No data are available with regard to overdosage of albendazole.

Treatment

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Albendazole is a benzimidazole carbamate with antiprotozoal and anthelmintic effects against intestinal and 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.

5.2 Pharmacodynamic Properties

ATC code: P02CA03

Intestinal Infections and Cutaneous Larva Migrans

Albendazole is active against intestinal parasites, including:

– ***Nematodes***
Ascaris lumbricoides (roundworm)
Trichuris trichiura (whipworm)
Enterobius vermicularis (pinworm/threadworm)
Ancylostoma duodenale (hookworm)
Necator americanus (hookworm)
Strongyloides stercoralis (threadworm)
Hookworms that cause cutaneous larva migrans

– ***Cestodes***
Hymenolepsis nana (dwarf tapeworm)
Taenia solium (pork tapeworm)
Taenia saginata (beef tapeworm)

– ***Trematodes***
Opisthorchis viverrini and *Clonorchis sinensis*

– ***Protozoa***
Giardia lamblia (*intestinalis* or *duodenalis*)

Systemic Helminth Infections

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 is also effective in the treatment of neurocysticercosis caused by larval infestation of *Taenia solium.*

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

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.

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

5.3 Pharmacokinetic Properties

Absorption

In humans, albendazole is poorly absorbed (less than 5%) following oral administration.

The systemic pharmacological effect of albendazole is augmented if the dose is administered with a fatty meal, which enhances the absorption by approximately five-fold.
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/L when taken with breakfast.

Metabolism

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.

Elimination

The plasma half-life of albendazole sulfoxide is 8.5 hours.

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.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Although albendazole treatment-related effects were observed in rat testes, no effects on litter size were observed in a male fertility study. Albendazole has been shown to be teratogenic and embryotoxic in rats and rabbits. Albendazole was negative for evidence of mutagenicity or genotoxicity in a panel of *in vitro* (including Ames inactivated and activated) 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 tumour formation was seen.

7. DESCRIPTION

Uncoated Chewable Tablet
Suspension

Tablet
Each uncoated chewable tablet contains:
Albendazole IP 400 mg
Colour: Sunset Yellow FCF
Excipients q.s.

Suspension
Each 10 ml contains:
Albendazole IP 400 mg in a flavoured syrup base.

List of Excipients

Tablets
Lactose, Starch, Polyvinylpyrrolidone, Sodium Lauryl Sulphate, Saccharin Sodium, Sunset Yellow FCF, Microcrystalline Cellulose, Sodium Starch Glycolate (Type A), Trusil Vanilla Special, Trusil Orange Special, Magnesium Stearate, Purified water.

Suspension
Polysorbate 80, Glycerin, Sorbitol Solution 70%, Methylparaben, Propylparaben, Sodium carboxymethyl cellulose, Sodium saccharin, American Ice cream flavour, Cardamom flavour, Purified water, Citric Acid Monohydrate.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

There are no relevant data available.

8.2 Shelf Life

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

Tablets: Alu-Alu blisters of tablets in a carton.

Suspension: Amber coloured glass bottle in a carton.

All presentations may not be marketed in India.

8.4 Storage and Handling Information Instruction

Tablets: Store in a dry place at a temperature not exceeding 30°C. Protect from light.
To be chewed before swallowing.

Suspension: Store in well closed container at a temperature not exceeding 30°C.
Shake well before use.

Keep out of reach of children.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or patients' caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contraindications of *ZENTEL*. Patients (and/or patients' caregiver) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office
Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Manufacturing License number is indicated on the label and packaging.

12. DATE OF REVISION

16-Sep-2024

Version ZEN/PI/IN/2024/01

Adapted from Albendazole GDS v28 dated 9 August 2024