# ZENTEL

## Albendazole

## QUALITATIVE AND QUANTITATIVE COMPOSITION

**Tablets:**
Each tablet contains 400 mg of albendazole.

**Oral suspensions:**
4 % w/v oral suspension 400 mg albendazole per 10 mL.
2 % w/v oral suspension 400 mg albendazole per 20 mL.

## CLINICAL INFORMATION

### Indications

*ZENTEL* is a benzimidazole carbamate with anthelmintic and antiprotozoal activity against the following 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 *Pharmacodynamics):*

- 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 *Pharmacodynamics*).

**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.

**Cystic Echinococcosis** (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

**Capillariasis** (*Capillaria philippinensis* infection)

**Gnathostomiasis** (caused by *Gnathostoma spinigerum* and related species)

**Trichinosis** (caused by *Trichinella spiralis* and *T. pseudospiralis*)

**Toxocariasis** (caused by *Toxocara canis* and other related species)

## Dosage and Administration

Pharmaceutical Form:

Tablet.
Oral suspension.

***INTESTINAL INFECTIONS AND CUTANEOUS LARVA MIGRANS***

**Dosage**

| Indications | Age | Dose | Period |
|---|---|---|---|
| - Ascariasis (roundworm infection)<br><br>- Enterobiasis (pinworm infection)<br><br>- Ancylostomiasis and necatoriasis (hookworm disease)<br><br>- Trichuriasis (whipworm infection) | Adults and children over 2 years of age. | 400 mg [one 400 mg tablet(s) or 10 mL 4% or 20 mL 2% suspension]# | Single dose. |
| | Children 1 to 2 years of age. | 200 mg (5 mL 4% or 10 mL 2% suspension) | Single dose. |
| - Suspected or confirmed strongyloidiasis (threadworm infection)<br><br>- Taeniasis (pork/beef | Adults and children over 2 years of age. | 400 mg (#see above) | One dose per day for 3 consecutive days.<br><br>†In cases of proven hymenolepsiasis, retreatment in 10 to 21 days is recommended. |

| | | | |
|---|---|---|---|
| tapeworm infection)<br><br>- Hymenolepiasis † (dwarf tapeworm infection) | | | |
| - Chlonorchiasis<br><br>- Opisthorchiasis<br><br>(liver fluke infections) | Adults and children over 2 years of age. | 400 mg (#see above) | One dose twice daily for 3 days. |
| - Cutaneous larva migrans [hookworm (animal origin) causing skin disease] | Adults and children over 2 years of age. | 400 mg | One dose per day for 1 to 3 days. |
| - Giardiasis | Children 2 to 12 years of age only. | 400 mg (#see above) | One dose per day for 5 days. |

**Method of Administration**

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

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

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.

**Special Patient Populations**

- **Elderly**

There are limited data on the use of *ZENTEL* 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***

**Dosage**

| **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. |

| **Infection** | **Patient Body Weight** | **Dose** | **Duration of Dosage** |
|---|---|---|---|
| *-Post-operative*<br><br>*-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.<br><br>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.<br><br>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). | |
| *-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). | |

| Infection | Patient Body Weight | Dose | Duration of Dosage |
|---|---|---|---|
| -*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.

| Infection | Dosage for Adults and Children | Duration of Dosage |
|---|---|---|
| **Capillariasis** | 400 mg | Daily for 10 days.<br># Normally only a single course of treatment is required, but further courses may be given if the clinical and parasitological findings remain positive |
| **Gnathostomiasis** | 400 mg | Daily for 10 to 20 days (# see above). |
| **Trichinosis** | 400 mg | Twice daily for 5 to 10 days (# see above). |

| | | |
|---|---|---|
| **Toxocariasis** | 400 mg | Twice daily for 5 to 10 days (# see above). |

**Method of Administration**

*ZENTEL* should be taken with meals (see *Pharmacokinetics*).

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 tablets may be crushed.

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

**Special Patient Populations**

- ***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 *ZENTEL* 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 *Warnings and Precautions* and *Adverse Reactions*).

## 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.

## Warnings and Precautions

***INTESTINAL INFECTIONS AND CUTANEOUS LARVA MIGRANS*** (short duration treatment at lower dose):

- **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 *Adverse Reactions*). 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 *Dosage and Administration* and *Adverse Reactions*).

- **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 (E110 or FD&C Yellow No 6) which may cause allergic-type reactions.
*ZENTEL* tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take *ZENTEL* tablets.
*ZENTEL* tablets contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

*ZENTEL* suspension contains benzoic acid which may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old). *ZENTEL* suspension contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’.

## Interactions

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

## Pregnancy and Lactation

### Fertility

There are no data on the effects of *ZENTEL* on human fertility.

No effects on male fertility have been observed in animal studies at clinically relevant exposures (see *Non-Clinical Information*).

### Pregnancy

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

### Lactation

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

## 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 *Adverse Reactions*).

## Adverse Reactions

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, pruritis 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 *Dosage and Administration* and *Warnings and Precautions*).

**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 *ZENTEL* 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

## Overdose

### Symptoms and signs

No data are available with regard to overdosage of *ZENTEL*.

### Treatment

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

# PHARMACOLOGICAL PROPERTIES

### Pharmacodynamics

### ATC code

P02CA03

### 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.

### Pharmacodynamic effects

***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*
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*, capillariasis caused by *Capillaria philippinensis* and gnathostomiasis caused by *Gnathostoma spinigerum* infestation.

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.

## Pharmacokinetics

### 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 peak 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.

## Clinical studies

No data available.

# NON-CLINICAL INFORMATION

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.

# PHARMACEUTICAL INFORMATION

## List of Excipients

**Tablets 400 mg:**
Lactose (see *Warnings and Precautions*)
Microcrystalline cellulose
Maize starch
Croscarmellose sodium
Povidone K30
Sodium lauryl sulphate
Sunset yellow FCF (E110 or FD&C Yellow No 6) (see *Warnings and Precautions*)
Sodium saccharin
Magnesium stearate
Flavourings

**Suspension (2%, 4%):**
Aluminium magnesium silicate
Carboxymethylcellulose sodium
Glycerin
Polysorbate 80
Sorbitan monolaureate
Potassium sorbate
Benzoic acid (see *Warnings and Precautions*)
Sorbic acid
Silicone antifoam 1510
Saccharin sodium
Flavourings

## Shelf-Life

The expiry date is indicated on the packaging.

## Storage

The storage conditions are detailed on the packaging.

## Nature and Contents of Container

***Tablets:*** Blister packs, polypropylene containers and cap.

***Oral suspensions:*** Glass/Plastic bottle with polypropylene cap.

## Incompatibilities

There are no special requirements for use on handling of this product.

## Use and Handling

Oral suspensions: Shake well before use.

Not all presentations are available in every country.

### Version number: GDS28/IPI12

### Date of issue: 09 August 2024

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**MANUFACTURING SITE**

**Tablet:**
Haleon South Africa (Pty) Ltd
11 Hawkins Avenue
Epping Industria One
Cape Town
Western Cape, 7450
Republic of South Africa

**Oral suspension:**
Manufactured and Packaged by:
Aspen Bad Oldesloe GmbH
Industriestrasse 32–36
23843 Bad Oldesloe
Germany