SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

HELMADOL 400 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains;

Active Substance **:** 400 mg albendazole,

Excipients **:**

Lactose monohydrate	315.60 mg
Sodium Lauryl Sulfate	2.00 mg
Sodium Starch Glycolate	20.00 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

Pink colored, oval, with a notch on one side, biconvex film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HELMADOL is indicated with infections listed below:

- Neurocysticercosis: HELMADOL is indicated for the treatment of parenchymal neurocysticercosis due to active lesions caused by larval forms of *Taenia solium* (pork tapeworm).
- Cystic hydatid disease: HELMADOL is indicated for the treatment of cystic hydatid disease of the liver, lung, and peritoneum, caused by the larval form of *Echinococcus granulosus* (dog tapeworm).

In patients given Albendazole for 3 cycles of therapy of 28 days each, non-infectious cyst contents in approximately 80 – 90%, cysts disappear in 30% and cysts reduce in 40% (reduction in cyst diameter of ≥ 25%).

When medically feasible, surgery is considered the treatment of choice for this disease. When administering HELMADOL in the pre- or post-surgical setting, optimal parasite killing ratio is achieved when 3 courses of therapy are given.

The efficacy of albendazole in the therapy of alveolar hydatid caused by *Echinononnus multilocularis* has not been clearly demonstrated in clinical studies.

Except these indications, HELMADOL is indicated in humans in treatment of intestinal and parenchymal helminthiasis infections caused by nematodes (roundworms) and cestodes (tapeworms) listed below.

Ascariasis: *Ascaris lumbricoides* (worm).
Enterobiasis (Oxyuriasis): *Enterobius* (*Oxyuris*) vermicularis (pinworm, oxyuride).
Hookworm disease: Albendazole is indicated in treatment of this disease caused by *Necator americanus* and *Ancylostoma duodenale*.
Strongyloidiasis: *Strongyloides stercoralis* (threadworm).
Trichuriasis: *Trichuris trichiura* (whipworm).
Capillariasis: *Capillaria philippinensis*.
Trichostrongyliasis: Albendazole is indicated in treatment of this disease caused by species of Trichostrongylus.
Taeniasis: Albendazole is indicated in treatment of intestinal helminthiasis caused by *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tapeworm).
Trichinosis: Albendazole is indicated in treatment of Trichinosis caused by *Trichinella spiralis.*
Chlonorchiasis: Albendazole is indicated in treatment of chlonorchiasis caused by *Chlonorchis sinensis* (Chinese liver fluke).
Giardiasis: Albendazole is indicated in treatment of giardiasis caused by Giardia species.

4.2 Posology and method of administration

Posology/ frequency and time of administration

HELMADOL dosage is dependent on the parasite infection involved and treatment diagram is presented below;

Indication	Weigh of Patient	Dosage	Duration of Therapy
Cystic hydatid disease	60 kg or greater	400 mg twice daily, with meals	This 28 day treatment period is repeated after a 14 day period without treatment for a total of 3 cycles.
	Less than 60 kg	15 mg/kg given in two equally divided doses twice daily with meals. (Maximum dose is 800 mg daily)	
	NOTE: In pre-surgical or post-surgical use, optimal cyst sterilization is achieved with repetition of the treatment course for 3 times.		
Neurocysticercosis	60 kg or greater	400 mg twice daily, with meals	8 to 30 Days
	Less than 60 kg	15 mg/kg given in two equally divided doses twice daily with meals. (Maximum dose is 800 mg daily)	

Other Helminthiasis Infections:

Dosage scheme for adults:

Ascariasis, Enterobiasis (Oxyuriasis), hookworm disease (*N.americanus*, *A.duodenale*), Trichuriasis, Trichostrongyliasis: Single dosage of 400 mg albendazole (1 x HELMADOL 400 mg Film Coated Tablets) should be taken in one go. Treatment may be repeated after 3 weeks.

Taeniasis (*T.saginata*, *T.solium*) and Strongyloidiasis: 400 mg albendazole (1 x HELMADOL 400 mg Film Coated Tablets) should be taken once daily for 3 days consecutively. Treatment may be repeated after 3 weeks.

Capillariasis: 200 mg albendazole (1/2 x HELMADOL 400 mg Film Coated Tablet) should be taken 2 times daily for 10 days.

Trichinosis: 400 mg albendazole (1 x HELMADOL 400 mg Film Coated Tablets) should be taken 2 times daily for 15 days.

Chlonorchiasis: 400 mg albendazole (1 x HELMADOL 400 mg Film Coated Tablets) should be taken 1 or 2 times daily for 7 days or 10 mg/kg albendazole should be taken 2 times daily for 7 days.

Giardiasis: 400 mg albendazole (1 x HELMADOL 400 mg Film Coated Tablets) should be taken daily for 3 days.

Method of administration:

HELMADOL should be taken with sufficient water (e.g. a glass of water) on a full stomach.

Additional Information Relating Special Populations:

Renal failure:

There is no data (See 5.2).

Liver failure:

In patients with extrahepatic obstruction (n = 5), the systemic availability of albendazole sulfoxide was increased, as indicated by a 2-fold increase in maximum serum concentration and a 7-fold increase in area under the curve. The rate of absorption/conversion and elimination of albendazole sulfoxide was prolonged and mean T_{max} became 10 hours and serum elimination half-life became 31.7 hours. Plasma concentrations of albendazole were in measurable levels in only 1 of 5 patients.

Pediatric population:

Experience in children under the age of 6 is limited.

Tablets may be swallowed with water after chewed or crushed.

Ascariasis, Enterobiasis (Oxyuriasis), hookworm disease (*N.americanus*, *A.duodenale*), Trichuriasis:

- In children up to 2 years of age: single dosage of 200 mg albendazole (1/2 x HELMADOL 400 mg Film Coated Tablets) only once. Treatment may be repeated after 3 weeks.
- In children older than 2 years: Dosage diagram for adults is applied.

Taeniasis ve Strongyloidiasis:

- In children up to 2 years of age: 200 mg albendazole (1/2 x HELMADOL 400 mg Film Coated Tablets) should be taken once daily for 3 days consecutively. Treatment may be repeated after 3 weeks.
- In children older than 2 years: Dosage diagram for adults is applied.

Capillariasis: 200 mg albendazole (1/2 x HELMADOL 400 mg Film Coated Tablets) two times daily

Trichostrongyliasis: Single dosage of 400 mg albendazole (1 x HELMADOL 400 mg Film Coated Tablet)

Cystic hydatid: 15 mg/kg albendazole is divided into two, one half is given in morning other is given at evening daily. Maximum daily dosage should not be more than 800 mg (2 x HELMADOL 400 mg Film Coated Tablets).

NOTE: In the pre-surgical and post-surgical use, optimal cyst sterilization is achieved with repetition of the treatment course for 3 times.

Geriatric population;

Experience in patients above the age of 65 is limited.

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.

4.3 Contraindications

HELMADOL is contraindicated in patients with known hypersensitivity to the benzimidazole class of compounds or any components of HELMADOL.

4.4 Special warnings and precautions for use

WARNINGS:

Rare fatalities associated with the use of albendazole have been reported due to granulocytopenia or pancytopenia. Albendazole has been shown to cause bone marrow suppression, aplastic anemia, and agranulocytosis in patients with and without underlying hepatic dysfunction. Blood counts should be monitored at the beginning of each 28-day cycle of therapy, and every 2 weeks while on therapy with albendazole in all patients. Patients with liver disease, including hepatic echinococcosis, appear to be more at risk for bone marrow suppression leading to pancytopenia, aplastic anemia, agranulocytosis, and leukopenia attributable to albendazole and warrant closer monitoring of blood counts. Albendazole should be discontinued in all patients if clinically significant decreases in blood cell counts occur.

Albendazole should be considered in pregnant women only if in clinical circumstances where no alternative management is appropriate. Patients should be warned against becoming pregnant for at least 1 month following cessation of albendazole therapy. If a patient becomes pregnant during albendazole therapy, medicine should be discontinued immediately. If pregnancy progresses while taking this drug, the patient should be apprised of the potential hazard to the fetus.

HELMADOL contains lactose. Patients with rare hereditary galactose intolarence, Lapp lactoce failure or glucose-galactose malabsorption problem should not use this drug.

HELMADOL contains less than 1 mmol (23 mg) sodium in each dose; with this dosage, no side effects expected related to sodium.

PRECAUTIONS:

General:

Patients being treated for neurocysticercosis should receive appropriate steroid and anticonvulsant therapy as required. Oral or intravenous corticosteroids should be considered to prevent cerebral hypertensive episodes during the first week of albendazole therapy.

Pre-existing neurocysticercosis may also be uncovered in patients treated with albendazole for other conditions. Neurological symptoms may be seen in patients (e.g. seizures, increased intracranial pressure and focal signs) as a result of an inflammatory reaction caused by death of a parasite within brain. Symptoms may occur just after treatment; in that case appropriate steroidal and anticonvulsant therapy should be started immediately.

Rarely, cysticercosis may develop in retina. Before initiating therapy for neurocysticercosis, the patient should be examined for the presence of retinal lesions. If such lesions are visualized, the need for anticysticeral therapy should be weighed against the possibility of retinal damage caused by albendazole-induced changes to the retinal lesion.

Informing patients:

Patients should be advised that:

- Some people, particularly children, may experience difficulties swallowing the tablets whole. In young children, the tablets should be crushed or chewed and swallowed with a drink of water.
- Albendazole may cause fetal harm; therefore, women of childbearing age should begin treatment after a negative pregnancy test.
- Women who take albendazole therapy should be warned against becoming pregnant while on albendazole or within 1 month of completing treatment.
- During albendazole therapy, because of possibility of harm to the liver or bone marrow routine (every two weeks) monitoring of blood counts and liver function tests should take place.
- Albendazole should be taken with food.

Laboratory Tets:

White Blood Cell Count:

Albendazole has been shown to cause occasional (less than 1% of treated patients) reversible reductions in total white blood cell count. Rarely, more significant reductions may be encountered including granulocytopenia, agranulocytosis, or pancytopenia. Blood counts should be performed at the start of each 28-day treatment cycle and every 2 weeks during each 28-day cycle in all patients. Patients with liver disease, including hepatic echinococcosis, appear to be more at risk of bone marrow suppression and warrant closer monitoring of blood counts.

Albendazole should be discontinued in all patients if clinically significant decreases in blood cell counts occur.

Liver Function:

In clinical trials, treatment with albendazole has been associated with mild to moderate elevations of hepatic enzymes in approximately 16% of patients. These elevations have generally returned to normal upon discontinuation of therapy. There have also been case reports of acute liver failure of uncertain severity and hepatitis.

Liver function tests (transaminases) should be performed at the beginning of each 28-day cycle and after every 2 weeks during treatment. If hepatic enzymes exceed twice the upper limit of normal, consideration should be given to discontinuing albendazole therapy based on individual

patient circumstances. Restarting albendazole treatment in patients, whose hepatic enzymes have normalized, is an individual decision that should take into account the risk/benefit of further albendazole usage. Laboratory tests should be performed frequently if albendazole treatment is restarted.

Patients with abnormal liver function test results are at increased risk for hepatotoxicity and bone marrow suppression. Therapy should be discontinued if liver enzymes are significantly increased or if clinically significant decreases in blood cell counts occur.

Theophylline:
Although single doses of albendazole do not inhibit theophylline metabolism, albendazole does induce cytochrome P450 1A in human hepatoma cells. Therefore, it is recommended that plasma concentrations of theophylline be monitored during and after treatment with albendazole.

4.5 Interaction with other medicinal products and other forms of interaction

Dexamethasone

Steady-state trough concentrations of albendazole sulfoxide were about 56% higher when 8 mg dexamethasone was coadministered with each dose of albendazole (15 mg/kg/day) in 8 neurocysticercosis patients.

Praziquantel

In the fed state, praziquantel (40 mg/kg) increased mean maximum plasma concentration and area under the curve of albendazole sulfoxide by about 50% in healthy subjects (n = 10) compared with a separate group of subjects (n = 6) given albendazole alone. Mean T_{max} and mean plasma elimination half-life of albendazole sulfoxide were unchanged. The pharmacokinetics of praziquantel was unchanged following coadministration with albendazole (400 mg).

Cimetidine

Albendazole sulfoxide concentrations in bile and cystic fluid were increased (about 2-fold) in hydatid cyst patients treated with cimetidine (10 mg/kg/day) (n = 7) compared with albendazole (20 mg/kg/day) alone (n = 12). Albendazole sulfoxide plasma concentrations were unchanged 4 hours after dosing.

Theophylline

No pharmacokinetic interaction was detected between albendazole (400 mg) and theophylline (aminophylline 5.8 mg/kg infused over 20 minutes) which are applied to 6 healthy subjects as a single oral dose.

Additional Information Relating Special Populations

Geriatric population;

Experience in patients above the age of 65 is limited.

The number of patients treated for either cystic hydatid disease or neurocysticercosis is limited, but no problems associated with an older population have been observed.

Pediatric population:

Experience in children under the age of 6 is limited. In hydatid disease, infection in infants and young children is uncommon, but no problems have been encountered in those who have been treated. In neurocysticercosis, infection is more frequently encountered. In 5 published studies involving 1 year old pediatric patients, no significant problems were encountered, and the efficacy appeared similar to the adult population.

4.6 Pregnancy and lactation

General advice

Its pregnancy category is C.

Women have childbearing potential / Contraception

Albendazole may cause fetal harm; therefore, women of childbearing age should begin treatment after a negative pregnancy test. Women of childbearing potential should be warned against becoming pregnant while on albendazole or within 1 month of completing treatment.

Pregnancy period

There is not sufficient data on using HELMADOL in pregnant women.

Studies in animals are insufficient on pregnancy and/or embryonal/fetal development and/or birth and/or postnatal development (see section 5.3). Albendazole has been shown to be teratogenic in pregnant rats and rabbits. Potential risk in human is not known.

HELMADOL may be used in pregnancy if advantages for mother are superior to risks for fetus.

Lactation

Albendazole is excreted in animal milk. It is not known whether it is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when albendazole is administered to a nursing woman.

Reproduction/ Fertility

Albendazole did not adversely affect male or female fertility in rats (See Section 5.3).

4.7 Effects on ability to drive and use machines

There is not any pharmacodynamic effect of albendazole obstructs ability to drive and use machines.

4.8 Undesirable effects

The frequencies of adverse reactions are ranked as in the following:
Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

The adverse event profile of albendazole differs between the groups that receive cystic hydatid and neurocysticercosis treatments. Adverse events with a frequency of ≥1% in both groups are described in the table below.

These symptoms were usually mild and resolved without treatment. Treatment discontinuations were predominantly due to leukopenia (0.7%) or hepatic function disorders (3.8%).

Adverse Event	Cystic hydatid	Neurocysticercosis
Abnormal liver function tests	15.6	<1.0
Abdominal pain	6.0	0
Nausea / Vomiting	3.7	6.2
Headache	1.3	11.0
Dizziness / Vertigo	1.2	<1.0
Raised intracranial pressure	0	1.5
Meningeal signs	0	1.0
Reversible alopecia	1.6	<1.0
Fever	1.0	0

The following adverse events were observed at an incidence of <1%.

Blood and Lymphatic System Disorders

Not common: Leukopenia

Rare: Granulocytopenia, pancytopenia, agranulocytosis and thrombocytopenia

Patients with liver disease, including hepatic echinococcosis, appear to be more at risk of bone marrow suppression.

Immune System Disorders

Not common: Hypersensitivity reactions, including itchiness and urticaria

Postmarketing Experience:

In addition to adverse events reported from clinical trials, the following events have been identified during world-wide post-approval use of albendazole. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to albendazole.

Blood and Lymphatic System Disorders

Not known: Aplastic anemia, bone marrow suppression, neutropenia.

Hepatobiliary Disorders

Not known: Elevations of hepatic enzymes (elevation of AST and ALT), toxic hepatitis, acute liver failure.

Skin and Subcutaneous Tissue Disorders

Not known: Erythema multiforme, Stevens-Johnson syndrome.

Renal and Urinary Disorders

Not known: Acute renal failure.

4.9 Overdose and Treatment

Significant toxicity and mortality were shown in male and female mice at doses exceeding 5,000 mg/kg; in rats, at estimated doses between 1,300 and 2,400 mg/kg; in hamsters, at doses exceeding 10,000 mg/kg; and in rabbits, at estimated doses between 500 and 1,250 mg/kg. In the animals, symptoms were demonstrated in a dose-response relationship and included diarrhea, vomiting, tachycardia, and respiratory distress.

One overdosage has been reported with albendazole in a patient who took at least 16 grams over 12 hours. No untoward effects were reported. In case of overdosage, symptomatic therapy and general supportive measures are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamical properties

Pharmacotherapeutic group: Antihelmintic medicines

ATC Code: P02CA03

The principal mode of action for albendazole is by its inhibitory effect on tubulin polymerization which results in the loss of cytoplasmic microtubules.

5.2 Pharmacokinetic properties

General Properties

Absorption:

Albendazole is poorly absorbed from the gastrointestinal tract due to its low aqueous solubility. Oral bioavailability appears to be enhanced when albendazole is coadministered with a fatty meal (estimated fat content 40 g) as evidenced by higher (up to 5-fold on average) plasma concentrations of albendazole sulfoxide as compared to the fasted state.

Maximal plasma concentrations of albendazole sulfoxide are typically achieved 2 to 5 hours after dosing and are on average 1.31 mcg/mL (range 0.46 to 1.58 mcg/mL) following oral doses of albendazole (400 mg) in 6 cystic hydatid patients, when administered with a fatty meal. Because albendazole turns to sulfoxide rapidly before passing through systemic circulation, albendazole concentration in plasma can be leave out or undetectable.

Distribution:

Albendazole sulfoxide is 70% bound to plasma protein and is widely distributed throughout the body; it has been detected in urine, bile, liver, cyst wall, cyst fluid, and cerebral spinal fluid (CSF). Concentrations in plasma were 3- to 10-fold and 2- to 4-fold higher than those simultaneously determined in cyst fluid and CSF, respectively. Limited *in vitro* and clinical data suggest that albendazole sulfoxide may be eliminated from cysts at a slower rate than observed in plasma.

Biotransformation:

Albendazole is rapidly converted in the liver to the primary metabolite, albendazole sulfoxide, which is further metabolized to albendazole sulfone and other primary oxidative metabolites that have been identified in human urine.

It is accepted that the medicine shows its affect by its primary metabolite albendazole sulfoxide. After albendazole treatment (200 mg taken 3 times a day) of 12 patients for 4 weeks; plasma albendazole sulfoxide concentrations were found 20% lower than the first half of the treatment. This indicates that albendazole may induce its own metabolism.

Elimination:

Following oral administration, albendazole has not been detected in human urine. Urinary excretion of albendazole sulfoxide is a minor elimination pathway as less than 1% of the dose is recovered in the urine. It is possible that a significant part of it is excreted in bile. Because biliary concentrations are similar to those achieved in plasma. Half-life of albendazole sulfoxide is found to be between 8 -12 hours in 25 healthy subjects with 14 cystic hydatid patients and 8 neurocysticercosis patients.

Linearity / Non-linear:

Plasma concentrations of albendazole sulfoxide elevates proportionally with dose, after taking the medicine in the therapeutic dose range with a fatty meal (43.1 g fat content).

Characteristic Features in Patients:

Renal Impairment:

The pharmacokinetics of albendazole in patients with impaired renal function has not been studied. However, 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.

Liver Impairment:

In patients with evidence of extrahepatic obstruction (n = 5), the systemic availability of albendazole sulfoxide was increased, as indicated by a 2-fold increase in maximum serum concentration and a 7-fold increase in area under the curve. The rate of absorption/conversion and elimination of albendazole sulfoxide appeared was prolonged and mean T_{max} became 10 hours and serum elimination half-life became 31.7 hours. Plasma concentrations of parent albendazole were measurable in only 1 of 5 patients.

Pediatrics Patients:

Following single-dose administration of 200 mg to 300 mg (approximately 10 mg/kg) albendazole to 3 fasted and 2 fed pediatric patients with cystic hydatid disease (age range 6 to 13 years), albendazole sulfoxide pharmacokinetic properties were similar to those observed in adults.

Geriatric Patients:

Although no studies have investigated the effect of age on albendazole sulfoxide pharmacokinetics, data obtained from 26 patients with cystic hydatid (up to 79 years) suggests that pharmacokinetics of albendazole is similar between elderly and young healthy subjects.

5.3 Preclinical safety data

In long-term carcinogenicity studies in mice and rats, an increase has been observed in tumor incidence.

In genotoxicity tests conducted on Chinese hamster and mice, albendazole is not found genotoxic.

Albendazole did not adversely affect male or female fertility in the rat at an oral dose of 30 mg/kg/day (0.32 times the recommended human dose based on body surface area in mg/m^2).

Teratogenic effect has been observed (to cause embryotoxicity and skeletal malformations) when albendazole was given to rats 10 and 30 mg/kg daily (0.10 times and 0.32 times the recommended human dose based on body surface area in mg/m^2, respectively), to rabbits 30 mg/kg daily (0.60 times the recommended human dose based on body surface area in mg/m^2) doses. In addition, in 30 mg/kg doses, while maternal toxicity (33% mortality) was observed in rabbits, no teratogenic effects were observed in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch pregelatinized
Sodium starch glycolate
Crospovidone
Plyvinyl pyrrolidone K25
Sodium lauryl sulphate
Talc
Magnesium stearate
Polyvinylalcohol

Plolyethylene glycol

Titanium dioxide (E171)

Red iron oxide (E172)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at room temperature below 30ºC.

6.5 Nature and contents of container

It is presented as 2 film coated tablets in PVC/ALU blister in a cardboard box package.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

World Medicine Ilac Sanayi ve Tic. A.Ş.

Bağcılar, Istanbul/TURKEY

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of First Authorization:

Renewal of the Authorization:

10. DATE OF REVISION OF THE TEXT