1.4.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Albendazole Chewable Tablets 400 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains 400 mg of Albendazole

Excipients: Each tablet contains 0.19 ml of Benzyl Alcohol.

This medicine contains Sodium.

For full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Tablet

A white to off-white coloured oblong shaped Biconvex, uncoated tablet with break line on one side and Plain on other Side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Single dose or short term courses of Albendazole are indicated in the treatment of single or mixed infestations of intestinal and tissue parasites, in adults and children over 2 years of age.

Clinical studies have shown Albendazole to be effective in the treatment of infections caused by: Enterobius vermicularis (pinworm/threadworm), Ascaris lumbricoides (roundworm), Ancylostoma duodenale and Necator americanus (hookworms), Trichuris trichiura (whipworm), Strongyloides stercoralis, animal hookworm larvae causing cutaneous larva migrans, and the liver flukes Opisthorchis viverrini and Clonorchis sinensis.

Albendazole is also indicated for the treatment of Hymenolepis nana and Taenia spp. (tapeworm) infections, when other susceptible helminths species are present. Treatment courses should be extended to 3 days.

For further information on the appropriate use of Albendazole Chewable tablets 400 mg in the context of mass drug administration for the control of intestinal worms, consideration should be given to official guidelines and recommendations.You are being given these tablets under a mass drug administration programme in which this medicine is administered depending on the risk of

infection in your community. Mass drug administration works by reducing the number of people in the community who are heavily infected with intestinal worms.

Official guidance will normally include WHO and local health authorities guidance.

4.2 Posology and method of administration

Posology

Route of administration: Oral.
Adults and Children (over two years):

- *Enterobius vermicularis, Ascaris lumbricoides, Ancylostoma duodenale, Necator americanus* and *Trichuris trichiura*: Albendazole 400 mg as a single dose, taken on an empty stomach.
- Suspected or confirmed *Strongyloides stercoralis* infestation: Albendazole 400mg once daily, taken on an empty stomach for three consecutive days. Patients should then be appropriately followed for at least 2 weeks to confirm cure.
- *Cutaneous larva migrans:* 400mg once daily, taken with food for one to three days has been reported to be effective.
- Suspected or confirmed *Taenia spp.* or *Hymenolepis nana* infestation, when other susceptible helminths species are present: Albendazole 400mg once daily, taken on an empty stomach for three consecutive days. If the patient is not cured after three weeks, a second course of Albendazole treatment is indicated. In cases of proven H. nana infestation, retreatment in 10-21 days is recommended.
- Mixed worm infestations including *Opisthorchis viverrini* and *Clonorchis sinensis:* 400mg twice a day, taken with food for three days is effective. Patients should be re-examined 1 month after treatment to confirm fluke eradication

Special populations

a) Elderly population: 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.

b) 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.

c) Hepatic impairment: Since Albendazole is rapidly metabolized 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 (transminases) prior to commencing Albendazole therapy should be carefully monitored.

d) Particular particular genotype: Not available

Paediatric population: The dose is same as that of adults, however, there is limited experience with ALBENDAZOLE in children under 2 years of age, and therefore use in this age group is not recommended.

4.3 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 and taken with small amount of water.

4.4 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 Chewable Tablets.

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.

4.5 Special warnings and precautions for use

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

Treatment with albendazole may uncover pre-existing neurocysticercosis, 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.

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

Mild to moderate elevations of liver enzymes have been reported with albendazole. In prolonged higher dose albendazole therapy for hydatid disease there have been rare reports of severe hepatic abnormalities associated with jaundice and histological hepatocelluler damage, which may be irreversible. Enzyme abnormalities usually normalise on discontinuation of treatment.

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 (greater than twice the upper limit of normal) or full blood count decreased by a clinically significant level. Albendazole treatment may be restarted when liver enzymes have returned to normal limits, but patients should be carefully monitored for a recurrence.

Case reports of hepatitis have also been received. Liver function tests should be obtained before the start of each treatment cycle and at least every two weeks during treatment.

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 leukopenia and therefore warrant closer monitoring of blood counts. Albendazole should be discontinued if clinically significant decreases in blood cell counts occur.

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.

There is a risk that treatment of *Taenia solium* infections may be complicated by cysticercosis, and appropriate measures should be taken to minimise this possibility.

Confirmation of eradication of many intestinal and tissue parasites is necessary after treatment. (see DOSAGE AND ADMINISTRATION).

4.6 Paediatric population

There is limited experience with ALBENDAZOLE in children under 2 years of age, therefore use in this age group is not recommended.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children. Do not give to your newborn baby (up to 4 weeks old), unless recommended by your doctor.

4.7 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.

4.8 Additional information on special populations

Use in Impaired Renal or Hepatic Function

The use of ALBENDAZOLE in patients with impaired renal or hepatic function has not been studied. However, caution should be used in patients with pre-existing liver disease, since ALBENDAZOLE is metabolised by the liver and has been associated with idiosyncratic hepatotoxicity.

4.9 Paediatric population

There is limited experience with ALBENDAZOLE in children under 2 years of age, therefore use in this age group is not recommended.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children. Do not give to your newborn baby (up to 4 weeks old), unless recommended by your doctor.

4.10 Fertility, Pregnancy and lactation

4.10.1 General principles

Pregnancy Category C. Albendazole has been shown to be teratogenic (to cause embryotoxicity and skeletal malformations) in pregnant rats and rabbits.The teratogenic response in the rat was shown at oral doses of 10 and 30 mg/kg/day (0.10 times and 0.32 times the recommended human dose based on body surface area in mg/m^2, respectively during gestation days 6 to 15 and in pregnant rabbits at oral doses of 30 mg/kg/day (0.60 times the recommended human dose based on body surface area in mg/m2) administered during gestation days 7 to 19. In the rabbit study, maternal toxicity (33% mortality) was noted at 30 mg/kg/day. In mice, no teratogenic effects were observed at oral doses up to 30 mg/kg/day (0.16 times the recommended human dose based on body surface area in mg/m^2), administered during gestation days 6 to 15.

There are no adequate and well-controlled studies of albendazole administration in pregnant women. Albendazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

4.10.2 Women of chilbearing potential/Contraception in males and females

In order to avoid administrating ALBENDAZOLE during early pregnancy, women of childearing age should initiate treatment during the first week of menstruation or negative pregnancy test.Women of childbearing age should be cautioned against becoming pregnant while on albendazole or within 1 month of completing treatment.

4.10.3 Pregnancy

Use in Pregnancy (Category D)

See CONTRAINDICATIONS. ALBENDAZOLE is contraindicated during pregnancy, and for one month prior to conception. In order to avoid administering albendazole during early pregnancy, women of child bearing age should initiate treatment during the first week of menstruation or after a negative pregnancy test.

The use of ALBENDAZOLE in human pregnancy has not been studied, but in animal studies it is teratogenic in more than one species. In animal studies oral treatment with maternotoxic doses of albendazole (30mg/kg/day) during the period of organogenesis was associated with multiple malformations in rats and ectrodactyly in rabbits. In one study in rats, an oral dose (10mg/kg/day) similar to the human therapeutic dose was not maternotoxic, but was associated with

microphthalmia and microfetalis. The latter occurred alone and together with multiple malformations including cranioschisis, talipes and renal agenesis. There is no information on the possible effect of albendazole on the human foetus.

4.10.4 Breastfeeding

Adequate human and animal data on use during lactation are not available. Therefore breast feeding should be discontinued during and for a minimum of 5 days after treatment.

4.10.5 Fertility

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)

4.11 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.

4.12 Undesirable effects

a) Summary of the safety profile

Rare fatalities associated with the use of ALBENDAZOLE have been reported due to granulocytopenia or pancytopenia (see PRECAUTIONS). 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 bonemarrow suppression leading to pancytopenia, aplastic anemia, agranulocytosis, and leukopeniaattributable to albendazole and warrant closer monitoring of blood counts. Albendazole shouldbe discontinued in all patients if clinically significant decreases in blood cell counts occur.Albendazole should not be used in pregnant women except in clinical circumstanceswhere no alternative management is appropriate. Patients should not become pregnant for at least 1 month following cessation of albendazole therapy. If a patient becomes pregnant while taking this drug, albendazole should be discontinued immediately. If pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus.

b) Tabulated list of adverse reactions

The following adverse events were observed during clinical studies and post-marketing surveillance (marked with asterisks (*). It should however be noted that causality has not necessarily been established for these events.

During prolonged higher dose albendazole therapy of hydatid disease there have also been reports of severe hepatic abnormalities, including jaundice and hepatocellular damage which may be irreversible.:

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

Use in intestinal infections and cutaneous *larva migrans* (short duration treatment at lower dose)

Blood and the lymphatic system disorders

Rare: Low red cell count

Immune system disorder

Rare: Hypersensitivity reactions including rash, pruritus and urticarial

Nervous system disorder

Uncommon: Headache*, dizziness

Gastrointestinal disorder

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

Uncommon: Diarrhoea

Hepatobiliary disorders

Rare: Elevations of hepatic enzymes

Skin and subcutaneous tissue disorders

Uncommon: Itchiness and/or skin rashes

Very rare: Erythema multiforme*, Stevens-Johnson syndrome*

Musculoskeletal & connective tissue disorder

Rare: Bone pain

Renal & urinary disorders

Rare: Proteinuria

Use in systemic helminth infections (longer duration of treatment at higher dose)

Blood and the lymphatic system disorders

Uncommon: Leucopenia,

Rare: Low red cell count

Very rare: Pancytopenia*, aplastic anaemia*, agranulocytosis*

Immune system disorders

Uncommon: Hypersensitivity reactions including rash, pruritus and urticarial

Nervous system disorder

Very common: Headache*

Common: Dizziness

Gastrointestinal disorder

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

Hepato-biliary disorder

Very common: Mild to moderate elevations of hepatic enzymes

Uncommon: Hepatitis*

During prolonged higher dose albendazole therapy of hydatid disease there have also been reports of severe hepatic abnormalities, including jaundice and hepatocellular damage which may be irreversible.

Skin and subcutaneous tissue disorders

Common: Reversible alopecia (thinning of hair, and moderate hair loss)*

Very rare: Erythema multiforme*, Stevens-Johnson syndrome*

Musculoskeletal & connective tissue disorder

Rare: Bone pain

Renal & Urinary disorder

Rare: Proteinuria

General disorders and administrative site conditions

Common: Fever*

Post-Marketing Data

During post-marketing surveillance, the following reactions have been reported additionally in temporal association with ALBENDAZOLE

Use in intestinal infections and Cutaneous *larva migrans* (short duration treatment at lower dose):

Nervous system disorder

Headache

Skin and subcutaneous tissue disorders

Erythema multiforme and Stevens-Johnson syndrome.

Use in systemic helminth infections (longer duration of treatment at higher doses):

Nervous system disorder

Headache

Skin and subcutaneous tissue disorders

Reversible alopecia (thinning of hair, and moderate hair loss), erythema multiforme and Stevens Johnson syndrome

Hepato-biliary disorder

Hepatitis

Blood and the lymphatic system disorders

Pancytopenia, aplastic anaemia and agranulocytosis

Patients with liver disease, including hepatic echinococcosis, appear to be more susceptible to bone

marrow suppression (see Precautions).

General disorders and administrative site conditions

Fever

c) Description of selected adverse reactions

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 causality and hepatitis.Liver function tests (transaminases) should be performed before the start of each treatment cycle and at least 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 off treatment 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 have been shown not to inhibit heophylline metabolism (see Drug Interactions), albendazole does induce cytochrome P450 1Ain human hepatoma cells. Therefore, it is recommended that plasma concentrations of theophylline be monitored during and after treatment.

d) Paediatric population:

Experience in children under the age of 6 years 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 pediatric patients as young as 1 year, no significant problems were encountered, and the efficacy appeared similar to the adult population.

e) Other special population :

Not available

4.13 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: Benzimidazole derivatives with anthelmintic effects against tissue parasites

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

Carcinogenicity and Mutagenicity

No evidence of carcinogenic activity was observed in mice given albendazole in the diet at doses up to 400mg/kg/day for 25 months. In rats, dietary administration of doses of 3.5, 7 and 20mg/kg/day did not affect the total incidence of adrenocortical tumours (adenoma plus carcinoma), however, in females there was an increased incidence of adrenocortical carcinomas.

Mutagenicity tests with bacterial cells and an assay of chromosomal damage *in vivo* have shown no clear evidence that albendazole has genotoxic activity. A cell transformation assay showed a slight dose-related increase in the transformation rate of cultured mouse cells in the presence of metabolic activation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Starch Glycolate
Microcrystalline Cellulose
Sodium Lauryl Sulphate
Maize Starch
Colloidal Anhydrous Silica
Aspartame
Mixed Fruit Flavour
Purified Talc
Magnesium Stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30 ^{0}C. Protect from moisture.

6.5 Nature and contents of container

A HDPE bottle with CR cap of 100 tablets. Affix printed label on HDPE bottle. Such one bottle pack in a printed carton along with leaflet.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

Marketing authorisation holder

Mepro Pharmaceuticals Pvt. Ltd

Address: 3rd floor, The International Building,

16 Maharshi Karve Marg, Churchgate,

Mumbai – 400 020.

Tel: +91 22 61477171

Fax: 022 66385339

Mail: dipesh@mepro.in

Manufacturer

Mepro Pharmaceuticals Pvt. Ltd

Unit-II, Q Road, Phase-IV, G.I.D.C,

Wadhwan City–363 035, Gujarat, INDIA

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

10. DATE OF REVISION OF THE TEXT