inhibition of the latter leading to less energy produced by the Krebs cycle. Due to diminished ATP production, the parasite is immobilized and eventually dies.

Some parasites have evolved to have some resistance to albendazole by having a different set of acids comprising β-tubulin, decreasing the binding affinity of albendazole.

4.2 Pharmacokinetic properties

Absorption and metabolism

Albendazole is poorly absorbed from the gastrointestinal tract due to its low aqueous solubility. Albendazole concentrations are negligible or undetectable in plasma as it is rapidly converted to the sulfoxide metabolite prior to reaching the systemic circulation.

The systemic anthelmintic activity has been attributed to the primary metabolite, albendazole sulfoxide. 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 hydatid disease patients, when administered with a fatty meal. Plasma concentrations of albendazole sulfoxide increase in a dose-proportional manner over the therapeutic dose range following ingestion of a fatty meal (fat content 43.1 g). The mean apparent terminal elimination half-life of albendazole sulfoxide typically ranges from 8 to 12 hours in 25 normal subjects, as well as in 14 hydatid and 8 neurocysticercosis patients.

Following 4 weeks of treatment with albendazole (200 mg three times daily), 12 patients' plasma concentrations of albendazole sulfoxide were approximately 20% lower than those observed during the first half of the treatment period, suggesting that albendazole may induce its own metabolism.

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.

Metabolism and Excretion

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. Following oral administration, albendazole has not been detected in human urine. Urinary excretion of albendazole sulfoxide is a minor elimination pathway with less than 1% of the dose recovered in the urine. Biliary elimination presumably accounts for a portion of the elimination as evidenced by biliary concentrations of albendazole sulfoxide similar to those achieved in plasma.

Special Populations

Patients with Impaired Renal Function: The pharmacokinetics of albendazole in patients with impaired renal function have 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.

Biliary Effects: 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 to be prolonged with mean Tmax and serum elimination half-life values of 10 hours and 31.7 hours, respectively. Plasma concentrations of parent albendazole were measurable in only 1 of 5 patients.

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

Elderly Patients: 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.

5. Clinical Particulars:

5.1 Therapeutic Indications:

Albendazole, also known as albendazolum, is a medication used for the treatment of a variety of parasitic worm infestations. It is useful for giardiasis, trichuriasis, filariasis, neurocysticercosis, hydatid disease, pinworm disease, and ascariasis, among others. It is taken by mouth.

5.2 Posology and method of administration:

Albendazole 400 mg chewable tablets may be crushed, chewed, or swallowed whole.

Adults and Children (over two years):

• Enterobius vermicularis, Ascaris lumbricoides, Ancylostoma duodenale, Necator americanus and Trichuris trichiura: 400mg as a single dose, taken on an empty stomach.

• Suspected or confirmed Strongyloides stercoralis infestation: albendazole 400 mg 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: 400 mg 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 400 mg 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: 400 mg twice a day, taken with food for three days is effective. Patients should be re-examined 1 month after treatment to confirm fluke eradication.

Method of administration

Oral use.

Do not swallow tablet whole. Chew the tablets completely before Swallowing.

5.3 Contraindications:

Albendazole should not be administered during pregnancy or in women thought to be pregnant. Albendazole has been shown to be teratogenic and embryotoxic in rats and rabbits. Women of childbearing age should be advised to take effective precautions

against conception during and within one month of completion of treatment with Albendazole. Albendazole is contraindicated in persons who are known to be hypersensitive to albendazole, other benzimidazole derivatives, or any component of the tablets.

5.4 Special warning and precaution for use:

Albendazole has been associated with mild to moderate elevations of hepatic enzymes. Hepatic enzymes generally normalise on discontinuation of treatment. Case reports of hepatitis have also been received. Liver function tests should be obtained before the start of each treatment cycle and at least every two weeks during treatment. If hepatic enzymes are significantly increased (greater than twice the upper limit of normal), albendazole should be discontinued. Treatment may be restarted when hepatic enzymes have returned to normal limits, but patients should be monitored for recurrence.

Albendazole has been shown to cause bone marrow suppression and therefore blood counts should be performed at the start and every two weeks during each 28-day cycle. Patients with liver disease, including hepatic echinococcosis, appear to be more susceptible to bone marrow suppression leading to pancytopenia, aplastic anaemia, agranulocytosis and leucopenia and therefore warrant closer monitoring of blood counts. Albendazole should be discontinued if clinically significant decreases in blood cell counts occur.

Precautions:

In order to avoid administering albendazole during early pregnancy, women of childbearing age should:

- Initiate treatment only after a negative pregnancy test. These tests should be repeated at least once before initiating the next cycle.
- Be advised to take effective precautions against conception during and within one month of completion of treatment with albendazole for a systemic infection.

Symptoms associated with an inflammatory reaction following death of the parasite may occur in patients receiving albendazole treatment for neurocysticercosis (e.g. seizures, raised intracranial pressure, focal signs). These should be treated with appropriate steroid and anticonvulsant therapy. Oral or intravenous corticosteroids are recommended to prevent cerebral hypertensive episodes during the first week of treatment.

Pre-existing neurocysticercosis may also be uncovered in patients treated with albendazole for other conditions, particularly in areas with high taenosis infection. Patients may experience neurological symptoms e.g. seizures, increased intracranial pressure and focal signs as a result of an inflammatory reaction caused by death of the parasite within the brain. Symptoms may occur soon after treatment, appropriate steroid and anticonvulsant therapy should be started immediately.

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

5.5 Interaction with other medicinal products and other forms of interaction:

Albendazole has been shown to induce liver enzymes of the cytochrome P450 system responsible for its own metabolism.

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

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

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

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

Grapefruit juice also increases the plasma levels of albendazole sulfoxide.

Other possible interactions

Because of possible alterations in cytochrome P450 activity, there is a theoretical risk of an interaction with the following

- Oral contraceptives
- Anticoagulants
- Oral hypoglycaemics
- Theophylline

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

5.6 Pregnancy and Lactation:

PREGNANCY

Albendazole should not be administered during pregnancy or in women thought to be pregnant

BREAST FEEDING

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

5.7 Effects on the 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.

5.8 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.

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

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

Immune system disorders: Hypersensitivity reactions including rash, pruritus and Urticaria

Nervous system disorders: Headache, Dizziness

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

Gastrointestinal disturbances have been associated with albendazole when treating patients with echinococcosis.

Hepato-biliary disorders: Mild to moderate elevations of hepatic enzymes and Hepatitis

Skin and subcutaneous tissue disorders: Reversible alopecia (thinning of hair, and moderate hair loss) and Erythema multiforme, Stevens-Johnson syndrome

General disorders and administrative site conditions: Fever

5.9 Overdose:

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

5.10 Pre-clinical Safety:

Not Applicable

6. Pharmaceutical Particulars:

6.1 List of Excipients:

- Microcrystalline cellulose
- Lactose
- Mannitol
- Sodium Carboxymethyl Cellulose
- Sodium benzoate
- Citric Acid Monohydrate
- Colour Sunset Yellow Supra
- Sodium starch glycolate
- Magnesium stearate
- Colloidal Anhydrous Silica
- Purified talc
- Aspartame
- Sodium Chloride
- Flavour Orange Powder EC

6.2 Incompatibilities: None

6.3 Shelf Life: 36 months.

6.4 Special Precautions for storage:

Store below 30° C. Protect from light and moisture.

6.5 Nature and contents of container:

1 tablet in a ALU-PVC blister. Such one blister along with insert packed in a carton.

6.6 Special precautions for disposal and other handling

None

7. Marketing Authorization Holder:

Ratnatris Pharmaceuticals Pvt. Ltd.
Survey no. 416, At- Indrad (382715)
Taluka-Kadi, Dist-Mehsana,
Gujarat, India

8. Marketing Authorization Number:

NA

9. Date of first Authorization /renewal of the authorization:

NA

10. Date of revision of text:

NA