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BENDEX Tablets (Albendazole)

Composition

BENDEX-400 Tablets
Each chewable uncoated tablet contains:
Albendazole ..... 400 mg
BENDEX Suspension
Each 5 mL contains:
Albendazole ..... 200 mg

Dosage Form/s

Tablet and suspension for oral administration

Pharmacology

Pharmacodynamics

The principal mode of action for albendazole is by its inhibitory effect on tubulin polymerization, which results in the loss of cytoplasmic microtubules.
In the specified treatment indications, albendazole appears to be active against the larval forms of the following organisms:
Echinococcus granulosus
Taenia solium

Pharmacokinetics

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 sulphoxide metabolite prior to reaching the systemic circulation. The systemic anthelmintic activity has been attributed to the primary metabolite, albendazole sulphoxide. Oral bioavailability appears to be enhanced when albendazole is co-administered with a fatty meal (estimated fat content: 40 g) as evidenced by higher (up to 5-fold on average) plasma concentrations of albendazole sulphoxide as compared with the fasted state.
Maximal plasma concentrations of albendazole sulphoxide 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 sulphoxide 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 sulphoxide typically ranged 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), plasma concentrations of albendazole

sulphoxide in 12 patients were approximately 20% lower than those observed during the first half of the treatment period, suggesting that albendazole may induce its own metabolism.

Albendazole sulphoxide 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 cerebrospinal 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 sulphoxide may be eliminated from cysts at a slower rate than observed in plasma.

Albendazole is rapidly converted in the liver to the primary metabolite, albendazole sulphoxide, which is further metabolized to albendazole sulphone 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 sulphoxide 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 sulphoxide similar to those achieved in plasma.

Special Populations

Patients with Renal Impairment: The pharmacokinetics of albendazole in patients with renal impairment has not been studied. However, since renal elimination of albendazole and its primary metabolite, albendazole sulphoxide, is negligible, it is unlikely that clearance of these compounds would be altered in these patients.

Biliary Effects: In patients with evidence of extra-hepatic obstruction (n = 5), the systemic availability of albendazole sulphoxide was increased, as indicated by a 2-fold increase in maximum serum concentration and a 7-fold increase in the area under the curve (AUC). The rate of absorption/conversion and elimination of albendazole sulphoxide appeared to be prolonged with mean T_{max} 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.

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

Geriatric: Although no studies have investigated the effect of age on albendazole sulphoxide pharmacokinetics, data in 26 hydatid cyst patients (up to 79 years of age) suggest pharmacokinetics similar to those in young healthy subjects.

Indications

Albendazole is indicated for the treatment of the following infections:

Neurocysticercosis

Albendazole is indicated for the treatment of parenchymal neurocysticercosis due to active lesions caused by larval forms of the pork tapeworm, *Taenia solium.*

Lesions considered responsive to albendazole therapy appear as non-enhancing cysts with no surrounding oedema on contrast-enhanced computerized tomography. Clinical studies in patients with lesions of this type demonstrate a 74% to 88% reduction in the number of cysts; 40% to 70% of albendazole-treated patients showed resolution of all active cysts.

Hydatid Disease

Albendazole is indicated for the treatment of cystic hydatid disease of the liver, lung, and peritoneum, caused by the larval form of the dog tapeworm, *Echinococcus granulosus*.

This indication is based on combined clinical studies, which demonstrated non-infectious cyst contents in approximately 80% to 90% of patients given albendazole for three cycles of therapy of 28 days each. Clinical cure (disappearance of cysts) was seen in approximately 30% of these patients, and improvement (reduction in cyst diameter of ≥25%) was seen in an additional 40%.

Note: When medically feasible, surgery is considered the treatment of choice for hydatid disease. When administering albendazole in the pre- or post-surgical setting, optimal killing of cyst contents is achieved when three courses of therapy have been given.

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

Albendazole can be indicated in the treatment of single or mixed intestinal parasites. Clinical studies have shown albendazole to be effective in the treatment of *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), *Enterobius vermicularis* (pinworm/threadworm), *Ancylostoma duodenale* and *Necator americanus* (hookworm), *Taenia spp.* (tapeworm) and *Strongyloides stercoralis.*

Dosage And Administration

Neurocysticercosis and Hydatid Cyst Disease

Dosing of albendazole will vary, depending upon which of the following parasitic infections is being treated. In young children, the tablets should be crushed or chewed and swallowed with plenty of water.

<table>
<tr><th>Indication</th><th>Patient Weight</th><th>Dose</th><th>Duration</th></tr>
<tr><td>Hydatid disease</td><td>60 kg or greater</td><td>400 mg twice daily, with meals</td><td rowspan="2">28-day cycle followed by a 14-day albendazole-free interval, for a total of three cycles</td></tr>
<tr><td></td><td>Less than 60 kg</td><td>15 mg/kg/day given in divided doses twice daily with meals (maximum total daily dose: 800 mg)</td></tr>
<tr><td></td><td colspan="3">NOTE: When administering albendazole in the pre- or post-surgical setting, optimal killing of cyst contents is achieved when three courses of therapy have been given.</td></tr>
<tr><td>Neurocysticercosis</td><td>60 kg or greater</td><td>400 mg twice daily, with meals</td><td>8 to 30 days</td></tr>
</table>

	Less than 60 kg	15 mg/kg/day given in divided doses twice daily with meals (maximum total daily dose: 800 mg)	

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 treatment.

In Single or Mixed Intestinal Parasites

In both adults and children over 2 years of age, 400 mg of albendazole can be given as a single dose.

The usual dose in children between 1 and 2 years of age is 200 mg as a single dose.

In heavy mixed infestation involving *Strongyloides* or *Taeniasis*, a single daily dose may be inadequate and the dose may be given for 3 consecutive days.

Giardiasis (Dose in Children Over 2 Years of Age)

A single 400 mg daily dose (two 200 mg tablets or 20 mL suspension) for 5 days.

Albendazole should be taken with food.

Note: If the patient is not cured after 3 weeks, a second course of treatment may be given. No special procedures, such as fasting or purging, are required.

Albendazole has not been adequately studied in children below 1 year of age.

Contraindications

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

Warnings And Precautions

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 anaemia and agranulocytosis in patients with and without underlying hepatic dysfunction. In all patients, blood counts should be monitored at the beginning of each 28-day cycle of therapy, and every 2 weeks while on therapy with albendazole. Patients with liver disease, including hepatic echinococcosis, appear to be more at risk for bone marrow suppression leading to pancytopenia, aplastic anaemia, agranulocytosis, and leucopenia 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 not be used in pregnant women except in clinical circumstances where 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 foetus.

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 anti-cysticeral therapy.
Pre-existing neurocysticercosis may also be uncovered in patients treated with albendazole for other conditions. 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.
Cysticercosis may, in rare cases, involve the 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 anti-cysticeral therapy should be weighed against the possibility of retinal damage caused by albendazole-induced changes to the retinal lesion.

White Blood Cells Count

Albendazole has been shown to cause occasional (less than 1% of treated patients) reversible reductions in the total white blood cells count. Rarely, more significant reductions may be encountered, including granulocytopenia, agranulocytosis or pancytopenia. In all patients, blood counts should be performed at the start of each 28-day treatment cycle and every 2 weeks during each 28-day cycle. 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 theophylline metabolism, albendazole does induce cytochrome (CY) P450 1A in human hepatoma cells. Therefore, it is recommended that plasma concentrations of theophylline be monitored during and after treatment with albendazole.

▶ Drug Interactions

Dexamethasone

Steady-state trough concentrations of albendazole sulphoxide were about 56% higher when 8 mg dexamethasone was co-administered 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 the AUC of albendazole sulphoxide 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 sulphoxide were unchanged. The pharmacokinetics of praziquantel was unchanged following co-administration with albendazole (400 mg).

Cimetidine

Albendazole sulphoxide 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 sulphoxide plasma concentrations were unchanged 4 hours after dosing.

Theophylline

The pharmacokinetics of theophylline (aminophylline 5.8 mg/kg infused over 20 minutes) was unchanged following a single oral dose of albendazole (400 mg) in 6 healthy subjects.

▶ Pregnancy

Pregnancy Category C

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 foetus.

▶ 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 mother.

▶ Paediatric Use

Experience in children below 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 five published studies involving paediatric patients as young as 1 year of age, no significant problems were encountered, and the efficacy appeared similar to the adult population.

▶ Geriatric Use

Experience in patients who are 65 years of age or older is limited. The number of patients treated for either hydatid disease or neurocysticercosis is limited, but no problems associated with an older population have been observed.

Undesirable Effects

The adverse event profile of albendazole differs between hydatid disease and neurocysticercosis. Adverse events occurring with a frequency of ≥1% in either disease are described in the table below.

These symptoms were usually mild and resolved without treatment. Treatment discontinuations were predominantly due to leucopenia (0.7%) or hepatic abnormalities (3.8% in hydatid disease). The following incidence reflects events that were reported by investigators to be at least possibly or probably related to albendazole.

Adverse Event Incidence ≥1% in Hydatid Disease and Neurocysticercosis

Adverse Event	Hydatid Disease	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 <1.0%:

Blood and Lymphatic System Disorders

Leucopenia. There have been rare reports of granulocytopenia, pancytopenia, agranulocytosis or thrombocytopenia. Patients with liver disease, including hepatic echinococcosis, appear to be more at risk of bone marrow suppression.

Immune System Disorders

Hypersensitivity reactions, including rash and urticaria.

Postmarketing Adverse Reactions

In addition to adverse events reported from clinical trials, the following events have been identified during worldwide 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

Aplastic anaemia,bone marrow suppression, neutropenia.

Hepatobiliary Disorders

Elevations of hepatic enzymes, hepatitis, acute liver failure.

Skin and Subcutaneous Tissue Disorders

Erythema multiforme, Stevens-Johnson syndrome.

Renal and Urinary Disorders

Acute renal failure.

Overdosage

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 diarrhoea, vomiting, tachycardia and respiratory distress.

One case of 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 (e.g. gastric lavage and activated charcoal) and general supportive measures are recommended.

Storage And Handling Instructions

Store in cool and dry place.

Packaging Information

BENDEX 400: Blister pack of 1 tablet
BENDEX: 10 ml glass bottle suspension
Last updated: November 2013
Last reviewed: November 2013

BENDEX Tablets
