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# BENDEX Plus Tablets (Ivermectin + Albendazole)

## Composition

BENDEX Plus Tablets
Each uncoated tablet contains:
Ivermectin, BP.....6 mg
Albendazole, IP.....400 mg

## Dosage Form

Tablet

## Pharmacology

### Pharmacodynamics

Albendazole
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*
Ivermectin
Ivermectin is a member of the avermectin class of broad-spectrum antiparasitic agents, which have a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels, which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).
The selective activity of compounds of this class is attributable to the facts that some mammals do not have glutamate-gated chloride channels and that the avermectins have a low affinity for mammalian ligand-gated chloride channels. In addition, ivermectin does not readily cross the blood-brain barrier in humans.
Ivermectin is active against various life-cycle stages of many but not all nematodes. It is active against the tissue microfilariae of *Onchocerca volvulus* but not against the adult form. Its activity against *Strongyloides stercoralisis* limited to the intestinal stages.

### Pharmacokinetics

Albendazole
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 to 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: 43.1g). 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.
Ivermectin
Following oral administration of ivermectin, plasma concentrations are approximately proportional to the dose. In two studies, after single 12mg doses of albendazole in fasting healthy volunteers (representing a

mean dose of 165 mcg/kg), the mean peak plasma concentrations of the major component (H2B1a) were 46.6 (±21.9) (range: 16.4 to 101.1) and 30.6 (±15.6) (range: 13.9 to 68.4) ng/mL,respectively, at approximately 4 hours after dosing. Ivermectin is metabolized in the liver, and ivermectin and/or its metabolites are excreted almost exclusively in the faeces over an estimated 12 days, with less than 1% of the administered dose excreted in the urine. The plasma half-life of ivermectin in humans is approximately 18 hours following oral administration.
The safety and pharmacokinetic properties of ivermectin were further assessed in a multiple-dose clinical pharmacokinetic study involving healthy volunteers. Subjects received oral doses of 30 to 120 mg (333 to 2,000 mcg/kg) ivermectin in a fasted state or 30 mg (333 to 600 mcg/kg) ivermectin following a standard high-fat (48.6 g of fat) meal. Administration of 30 mg ivermectin following a high-fat meal resulted in an approximate 2.5-fold increase in bioavailability relative to administration of 30 mg ivermectin in the fasted state.
*In vitro* studies using human liver microsomes and recombinant cytochrome (CY) P450 enzymes have shown that ivermectin is primarily metabolized by CYP3A4. Depending on the *in vitro* method used, CYP2D6 and CYP2E1 were also shown to be involved in the metabolism of ivermectin but to a significantly lower extent compared to CYP3A4. The findings of *in vitro* studies using human liver microsomes suggest that clinically relevant concentrations of ivermectin do not significantly inhibit the metabolizing activities of CYP3A4, CYP2D6, CYP2C9, CYP1A2, and CYP2E1.

## Indications

For the treatment of nematode infestations.

## Dosage And Administration

1 tablet once daily. Oral Suspension

## Contraindications

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

## Warnings And Precautions

### Albendazole

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.
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.
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.
Although single doses of albendazole have been shown not to inhibit theophylline metabolism, albendazole does induce CYP450 1A in human hepatoma cells. Therefore, it is recommended that plasma concentrations of theophylline be monitored during and after treatment with albendazole.

## Ivermectin

Historical data have shown that microfilaricidal drugs, such as diethylcarbamazine citrate (DEC-C), might cause cutaneous and/or systemic reactions of varying severity (the Mazzotti reaction) and ophthalmological reactions in patients with onchocerciasis. These reactions are probably due to allergic and inflammatory responses to the death of microfilariae. Patients treated with ivermectin for onchocerciasis may experience these reactions in addition to clinical adverse reactions possibly, probably, or definitely related to the drug itself.
The treatment of severe Mazzotti reactions has not been subjected to controlled clinical trials. Oral hydration, recumbency, intravenous normal saline, and/or parenteral corticosteroids have been used to treat

postural hypotension. Antihistamines and/or aspirin have been used for most mild-to-moderate cases.
After treatment with microfilaricidal drugs, patients with hyperreactive onchodermatitis (sowda) may be more likely than others to experience severe adverse reactions, especially oedema and aggravation of onchodermatitis.Rarely, patients with onchocerciasis who are also heavily infected with *Loa loa may* develop a serious or even fatal encephalopathy either spontaneously or following treatment with an effective microfilaricide.
In these patients, the following adverse experiences have also been reported: pain (including neck and back pain), red eye, conjunctival haemorrhage, dyspnoea, urinary and/or faecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma. This syndrome has been seen very rarely following the use of ivermectin. In individuals who warrant treatment with ivermectin for any reason and have had significant exposure to *Loa loa*-endemic areas of West or Central Africa, pre-treatment assessment for loiasis and careful post-treatment follow-up should be implemented.

## Information for Patients

Ivermectin should be taken on an empty stomach with water.
*Strongyloidiasis:* The patient should be reminded of the need for repeated stool examinations to document clearance of infection with Strongyloides stercoralis.
*Onchocerciasis:* The patient should be reminded that treatment with ivermectin does not kill the adult Onchocerca parasites and, therefore, repeated follow-up and retreatment is usually required.

▶ Drug Interactions

Albendazole
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.
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).
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.
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.
Ivermectin
Postmarketing reports of increased International Normalized Ratio(INR) have been, rarely, reported when ivermectin was co-administered with warfarin.

▶ Pregnancy

Pregnancy Category C
There are, however, no adequate and well-controlled studies in pregnant women.
The albendazole and ivermectin combination should not be used during pregnancy since safety in pregnancy has not been established.

▶ 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.
Ivermectin is excreted in human milk in low concentrations. Treatment of mothers who intend to breastfeed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the newborn.

## Undesirable Effects

### Albendazole

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%:
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.

## Ivermectin

### Strongyloidiasis

In four clinical studies involving a total of 109 patients given either one or two doses of 170 to 200 mcg/kg of ivermectin, the following adverse reactions were reported as possibly, probably, or definitely related to ivermectin:
*Body as a Whole:* Asthenia/fatigue (0.9%), abdominal pain (0.9%).
*Gastrointestinal:* Anorexia (0.9%), constipation (0.9%), diarrhoea (1.8%), nausea (1.8%), vomiting (0.9%).
*Nervous System/Psychiatric:* Dizziness (2.8%), somnolence (0.9%), vertigo (0.9%), tremor (0.9%).
*Skin:* Pruritus (2.8%), rash (0.9%), and urticaria (0.9%).
In comparative trials, patients treated with ivermectin experienced more abdominal distention and chest discomfort than patients treated with albendazole. However, ivermectin was better tolerated than thiabendazole in comparative studies involving 37 patients treated with thiabendazole.
The Mazzotti-type and ophthalmologic reactions associated with the treatment of onchocerciasis or the disease itself would not be expected to occur in strongyloidiasis patients treated with ivermectin.

### Laboratory Test Findings

In clinical trials involving 109 patients given either one or two doses of 170 to 200 mcg/kg ivermectin, the following laboratory abnormalities were seen regardless of drug relationship: elevation in ALT and/or AST (2%), decrease in leucocyte count (3%). Leucopenia and anaemia were seen in 1patient.

### Onchocerciasis

In clinical trials involving 963 adult patients treated with 100 to 200 mcg/kg ivermectin, worsening of the following Mazzotti reactions during the first 4 days post-treatment were reported: arthralgia/synovitis (9.3%), axillary lymph node enlargement and tenderness (11.0% and 4.4%,respectively), cervical lymph node enlargement and tenderness (5.3% and 1.2%, respectively), inguinal lymph node enlargement and tenderness (12.6% and 13.9%, respectively), other lymph node enlargement and tenderness (3.0% and 1.9%, respectively), pruritus (27.5%), skin involvement, including oedema, papular and pustular or frank urticarial rash (22.7%), and fever (22.6%).
In clinical trials, ophthalmological conditions were examined in 963 adult patients before treatment, at day 3, and months 3 and 6 after treatment with 100 to 200 mcg/kg ivermectin. Changes observed were primarily deterioration from baseline 3 days post-treatment. Most changes either returned to baseline condition or improved over baseline severity at the month 3 and 6 visits. The percentages of patients with worsening of the following conditions at day 3, month 3 and 6, respectively, were limbitis(5.5%, 4.8%, and 3.5%) and punctate opacity(1.8%, 1.8%, and 1.4%). The corresponding percentages for patients treated with placebo were limbiti: (6.2%, 9.9%, and 9.4%) and punctate opacity(2.0%, 6.4%, and 7.2%).
In clinical trials involving 963 adult patients who received 100 to 200 mcg/kg ivermectin, the following clinical adverse reactions were reported as possibly, probably, or definitely related to the drug in ≥1% of the patients: facial oedema (1.2%), peripheral oedema (3.2%), orthostatic hypotension (1.1%), and tachycardia (3.5%). Drug-related headache and myalgia occurred in
A similar safety profile was observed in an open study in paediatric patients aged 6 to 13 years.
The following ophthalmological side effects do occur due to the disease itself but have also been reported after treatment with ivermectin: abnormal sensation in the eyes, eyelid oedema, anterior uveitis,

conjunctivitis, limbitis, keratitis, and chorioretinitis or choroiditis. These have rarely been severe or associated with loss of vision and have generally resolved without corticosteroid treatment.
Laboratory Test Findings
In controlled clinical trials, the following laboratory adverse experiences were reported as possibly, probably, or definitely related to the drug in ≥1% of the patients: eosinophilia (3%) and haemoglobin increase (1%)
Postmarketing Experience
The following adverse reactions have been reported since the drug was registered overseas:
*Onchocerciasis*
Conjunctival haemorrhage.
*All Indications*
Hypotension (mainly orthostatic hypotension), worsening of bronchial asthma, toxic epidermal necrolysis, Stevens-Johnson syndrome, seizures, hepatitis, elevation of liver enzymes, and elevation of bilirubin.

## Overdosage

### Albendazole
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 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.
### Ivermectin
Significant lethality was observed in mice and rats after single oral doses of 25 to 50 mg/kg and 40 to 50 mg/kg, respectively. No significant lethality was observed in dogs after single oral doses of up to10 mg/kg. At these doses, the treatment-related signs that were observed in these animals include ataxia, bradypnoea, tremors, ptosis, decreased activity, emesis, and mydriasis.
In accidental intoxication with, or significant exposure to, unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, inhalation, injection or exposure to body surfaces, the following adverse effects have been reported most frequently: rash, oedema, headache, dizziness,asthenia, nausea, vomiting, and diarrhoea. Other adverse effects that have been reported include seizure, ataxia, dyspnoea, abdominal pain, paraesthesia, urticaria, and contact dermatitis.
In case of accidental poisoning, supportive therapy, if indicated, should include parenteral fluids and electrolytes, respiratory support (oxygen and mechanical ventilation if necessary) and pressor agents if clinically significant hypotension is present. Induction of emesis and/or gastric lavage as soon as possible, followed by purgatives and other routine anti-poison measures, may be indicated if needed to prevent absorption of the ingested material.

## Storage And Handling Instructions

Store in cool and dry place.

## Packaging Information

BENDEX Plus: Alu Alu blister strip contains one tablet

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# BENDEX Plus Tablets

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