For the use only of a Registered Medical Practitioner only

**ALMINTH PLUS**
**(Ivermectin & Albendazole Tablets)**

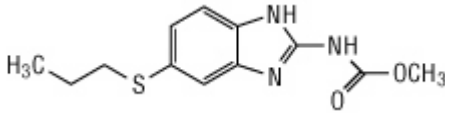
## COMPOSITION

Each uncoated tablet contains:
Ivermectin I.P..... 6 mg
Albendazole I.P. .....400 mg

## DESCRIPTION

***Albendazole***

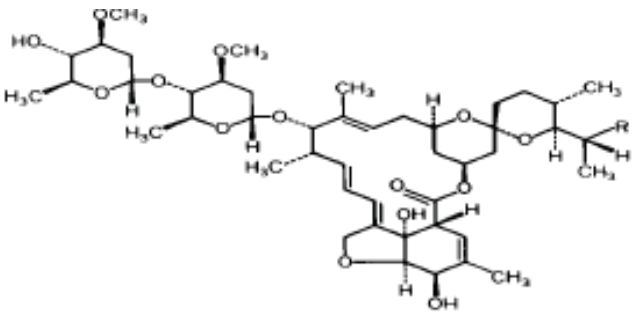
Albendazole is an orally administered broad-spectrum anthelmintic. Chemically, it is methyl 5-(propylthio)-2-benzimidazolecarbamate. Its molecular formula is $C_{12}H_{15}N_3O_2S$. Its molecular weight is 265.34.
It has the following chemical structure:




Albendazole is a white to off-white powder. It is soluble in dimethylsulfoxide, strong acids, and strong bases. It is slightly soluble in methanol, chloroform, ethyl acetate, and acetonitrile. Albendazole is practically insoluble in water. Each white to off-white, film-coated tablet contains 200mg of albendazole. Inactive ingredients consist of: carnauba wax, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium saccharin, sodium starch glycolate, and starch

***Ivermectin***

Ivermectin is a semisynthetic, anthelmintic agent for oral administration. Ivermectin is derived from the avermectins, a class of highly active broad-spectrum, anti-parasitic agents isolated from the fermentation products of Streptomyces avermitilis. Ivermectin is a mixture containing at least 90% 5-Odemethyl- 22,23-dihydroavermectin A1a and less than 10% 5-O-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)avermectinA1a, generally referred to as 22,23-dihydroavermectin B1a and B1b, or H2B1a and H2B1b, respectively. The respective empirical formulas are $C_{48}H_{74}O_{14}$ and $C_{47}H_{72}O_{14}$, with molecular weights of 875.10 and 861.07, respectively.
The structural formulas are




Component $B_{1a}$, R = $C_2H_5$ Component $B_{1b}$, R = $CH_3$

## CLINICAL PHARMACOLOGY

### Pharmacodynamics

***Albendazole***

Mechanism of action:

Benzimidazoles are thought to act against nematodes by inhibiting microtubule synthesis. Albendazole also has larvicidal effects in hydatid disease, cysticercosis, ascariasis, and hookworm infection and ovicidal effects in ascariasis, ancylostomiasis, and trichuriasis

***Ivermectin:***

Ivermectin probably binds to glutamate-activated $Cl^-$ channels found in nematode nerve or muscle cells, which causes hyperpolarization by increasing permeability of chloride ions through the cell membrane; this results in paralysis of the parasite.

Ivermectin is effective and highly potent against at least some developmental stages of many parasitic nematodes and insects that affect animals and humans. The drug immobilizes affected organisms by inducing a tonic paralysis of the musculature. Studies of *Caenorhabditis elegans* indicate that avermectins induce paralysis *via* a group of glutamate-gated $Cl^-$ channels found only in invertebrates. There is close correlation among activation and potentiation by avermectins and milbemycin D of glutamate-sensitive $Cl^-$ current, nematicidal activity, and membrane binding affinity. Moreover, glutamate-gated $Cl^-$ channels are expressed in the pharyngeal muscle cells of these worms, consistent with the marked and potent inhibitory effect of avermectins on the feeding behavior of the organisms.

The basis for resistance or relative unresponsiveness to avermectin action shown by different nematodes, especially those species parasitizing livestock, is complex. Several different avermectin-"resistant" developmental and physiological phenotypes have been described, but definitive relationships among these phenotypes and native avermectin receptor subtypes, locations, Alterations in genes encoding ATP-dependent P-glycoprotein transporters that bind avermectins and in those encoding putative components of the glutamate-gated $Cl^-$ channel have been associated with the development of resistance in *Haemonchus contortus*. A large increase in low-affinity glutamate binding has been detected in ivermectin-resistant nematodes, but how this relates to drug resistance is unclear. Glutamate-gated $Cl^-$ channels probably are one site of ivermectin action in insects and crustaceans, too. Avermectins also bind with high affinity to gamma-aminobutyric acid (GABA)-gated and other ligand-gated $Cl^-$ channels in nematodes such as *Ascaris* and in insects, but the physiological consequences are less well defined. Lack of high-affinity avermectin receptors in cestodes and trematodes may explain why these helminths are not sensitive to Ivermectin

## PHARMACOKINETICS

***Albendazole***

**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 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 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 200mg to 300mg (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. Microbiology: 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***
Following oral administration of ivermectin, plasma concentrations are approximately proportional to the dose. In two studies, after single 12-mg doses of Ivermectin 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: 16.4-101.1) and 30.6 (±15.6) (range: 13.9-68.4) 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 feces over an estimated 12 days, with less than 1% of the administered dose excreted in the urine. The plasma half-life of ivermectin in man 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 2000mcg/kg) ivermectin in a fasted state or 30 mg (333 to 600mcg/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 2.5fold increase in bioavailability relative to administration of 30 mg ivermectin in the fasted state.

*In vitro* studies using human liver microsomes and recombinant CYP450 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.

***Microbiology***
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 stercoralis is limited to the intestinal stages.

***Clinical Studies***

Strongyloidiasis:

Two controlled clinical studies using albendazole as the comparative agent were carried out in international sites where albendazole is approved for the treatment of strongyloidiasis of the gastrointestinal tract, and three controlled studies were carried out in the U.S. and internationally using thiabendazole as the comparative agent. Efficacy, as measured by cure rate, was defined as the absence of larvae in at least two follow-up stool examinations 3 to 4 weeks post-therapy. Based on this criterion, efficacy was significantly greater for ivermectin (a single dose of 170 to 200mcg/kg) than for albendazole (200 mg b.i.d. for 3 days). ivermectin administered as a single dose of 200mcg/kg for 1 day was as efficacious as thiabendazole administered at 25 mg/kg b.i.d. for 3 days.

*Onchocerciasis*

The evaluation of ivermectin in the treatment of onchocerciasis is based on the results of clinical studies involving 1278 patients. In a double-blind, placebo-controlled study involving adult patients with moderate to severe onchocercal infection, patients who received a single dose of 150 mcg/kg ivermectin experienced an 83.2% and 99.5% decrease in skin microfilariae count (geometric mean) 3 days and 3 months after the dose, respectively. A marked reduction of >90% was maintained for up to 12 months after the single dose. As with other microfilaricidal drugs, there was an increase in the microfilariae count in the anterior chamber of the eye at day 3 after treatment in some patients. However, at 3 and 6 months after the dose, a significantly greater percentage of patients treated with ivermectin had decreases in microfilariae count in the anterior chamber than patients treated with placebo.

In a separate open study involving pediatric patients ages 6 to 13 (n=103; weight range: 17-41 kg), similar decreases in skin microfilariae counts were observed for up to 12 months after dosing

**INDICATIONS AND USAGE**

For the treatment of intestinal helminthes and suppression of microfilaraemia especially with bancrofti infections

**CONTRAINDICATIONS**

***Albendazole***

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

***Ivermectin:***

Ivermectin is contraindicated in patients who are hypersensitive to any component of this product.

**WARNINGS AND PRECAUTION**

***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 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 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 fetus.

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 anticysticeral 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 anticysticeral therapy should be weighed against the possibility of retinal damage caused by albendazole-induced changes to the retinal lesion.

***Ivermectiin***

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 edema 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 hemorrhage, dyspnea, urinary and/or fecal 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

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.

## DOSAGE AND ADMINISTRATION

Suppression of microfilaraemia: daily one tablet once a day.
Intestinal Helminths: one tablet as a single dose for infection with intestinal helminths

## DRUG INTERACTION

***Albendazole***

*Dexamethasone**:***

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

*Praziquantel**:***

In the fed state, praziquantel (40mg/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 Tmax and mean plasma elimination half-life of albendazole sulfoxide were unchanged. The pharmacokinetics of praziquantel were 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:*

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

***Ivermectiin***

Post-marketing reports of increased INR (International Normalized Ratio) have been rarely reported when ivermectin was co-administered with warfarin.

## ADVERSE EVENT

***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 leukopenia (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:*
Leukopenia. 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 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.

*Skin and Subcutaneous Tissue Disorders:* Erythema multiforme, Stevens-Johnson syndrome.

*Renal and Urinary Disorders: Acute renal failure.*

***Ivermectin:***
In four clinical studies involving a total of 109 patients given 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%), diarrhea (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 leukocyte count (3%). Leukopenia and anemia were seen in one patient.

In clinical trials involving 963 adult patients treated with 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 edema, 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 200mcg/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 opacity: 1.8%, 1.8%, and 1.4%. The corresponding percentages for patients treated with placebo were: limbitis: 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 200mcg/kg ivermectin, the following clinical adverse reactions were reported as possibly, probably, or definitely related to the drug in ≥1% of the patients: facial edema (1.2%), peripheral edema (3.2%), orthostatic hypotension (1.1%), and tachycardia (3.5%). Drug-related headache and myalgia occurred in <1% of patients (0.2% and 0.4%, respectively). However, these were the most common adverse experiences reported overall during these trials regardless of causality (22.3% and 19.7%, respectively).

A similar safety profile was observed in an open study in pediatric patients ages 6 to 13

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 edema, 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 hemoglobin increase (1%).

**Post-Marketing Experience**
The following adverse reactions have been reported since the drug was registered overseas:
*Onchocerciasis*
Conjunctival hemorrhage

*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 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.

***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 to 10 mg/kg. At these doses, the treatment-related signs that were observed in these animals include ataxia, bradypnea, 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, edema, headache, dizziness, asthenia, nausea, vomiting, and diarrhea. Other adverse effects that have been reported include: seizure, ataxia, dyspnea, abdominal pain, paresthesia, 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 ingested material.

**EXPIRY DATE**
Do not use later than the date of expiry.

**STORAGE**
Store below 25°C in a dry place. Protect from light.

**PRESENTATION**
Blister of 1 Tablet.

**MARKETED BY**


TORRENT PHARMACEUTICALS LTD.
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