



MEBENDAZOLE

C7ED

Antiox® 50 mg/mL Chocolate suspension

Anthelmintic

FORMULATION

Each mL of the suspension contains 50 mg mebendazole.

The inactive ingredients are sucrose, microcrystalline cellulose and sodium carmellose, methylcellulose, methyl and propyl paraben, ethanol refined, polysorbate 20, tetraome orange diluted with ethanol, chocolate flavor, citric acid and purified water.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Mechanism of Action

In therapeutic indications mebendazole acts locally in the lumen of the gut by interfering with cellular tubulin formation in the intestines of worms. Mebendazole binds specifically to tubulin and causes ultrastructural degenerative changes in the intestine. As a result, the glucose uptake and the digestive functions of the worm are disrupted to such an extent that an autolytic process occurs.

Pharmacokinetic Properties

Absorption

Following oral administration, <10% of the dose reaches the systemic circulation, due to incomplete absorption and to extensive pre-systemic metabolism (first-pass effect). The majority of an orally administered dose remains in the gastrointestinal tract. Maximum plasma concentrations are generally seen 2 to 4 hours after administration.

Dosing with a high fat meal increases the bioavailability of mebendazole, although the overall effect of food on the amount of drug remaining in the gastrointestinal tract is not expected to be substantial.

Distribution

The plasma protein binding of mebendazole is 90 to 95%. The volume of distribution is 1 to 2 L/kg, indicating that mebendazole penetrates areas outside the vascular space. This is supported by data in patients on chronic mebendazole therapy (e.g., 40 mg/kg/day for 3-21 months) that show drug levels in tissue.

Metabolism

Orally administered mebendazole is extensively metabolized primarily by the liver. Plasma concentrations of its major metabolites (hydrolyzed and reduced forms of mebendazole) are higher than those of mebendazole. Impaired hepatic function, impaired metabolism, or impaired biliary elimination may lead to higher plasma levels of mebendazole.

Elimination

Mebendazole, the conjugated forms of mebendazole, and its metabolites likely undergo some degree of enterohepatic recirculation and are excreted in the urine and bile. The apparent elimination half-life after an oral dose ranges from 3 to 6 hours in most patients.

Steady-state pharmacokinetics

During chronic dosing (e.g., 40 mg/kg/day for 3-21 months), plasma concentrations of mebendazole and its major metabolites increase, resulting in approximately 3-fold higher exposure at steady-state compared to single dosing.

Specific populations

Pediatric

Based on a limited number of blood samples, the pharmacokinetic results following single-dose administration of a 500 mg mebendazole chewable tablet to pediatric patients (age 1 to 16 years) with single or mixed infections of *T. trichiura* and/or *A. lumbricoides* indicated that children aged 1 to 3 years have higher systemic exposure than adults.

NON-CLINICAL INFORMATION

The single-dose toxicity evaluations in multiple species revealed that mebendazole was well tolerated and has a large margin of safety. Repeated-dose, oral, chronic toxicity results in rats, at toxic dose levels of 40 mg/kg (240 mg/m²) and above, showed altered liver weights with some slight centrilobular swelling and hepatocellular vacuolation, and altered testicular weights with some tubular degeneration, desquamation and marked inhibition of spermatogenic activity.

Carcinogenicity and Mutagenicity

No carcinogenic effects were observed in the mouse or rat. No mutagenic activity was shown in *in vitro* gene-mutagenicity studies.

In vivo tests revealed no structural chromosome damaging activity. Micronucleus test results have shown aneugenic effects in mammalian somatic cells above a threshold plasma concentration of 115 ng/mL.

Reproductive Toxicology

At maternal toxic doses, embryo toxic and teratogenic activity has been shown in pregnant rats at a single dose of 10 mg/kg (60 mg/m²) and above. Teratogenic and fetotoxic effects have also been observed in mice at maternally toxic doses of 10 mg/kg (60 mg/m²) and higher. No harmful effects on reproduction were noted in other animal species tested.

Fertility

Male rat fertility was not affected with doses up to 40 mg/kg (240 mg/m²) for 60 days. When female rats were dosed at up to 10 mg/kg body weight for 14 days before gestation and during pregnancy, no significant effect upon fetuses and offspring were observed. However, when female rats were dosed at 40 mg/kg (240 mg/m²) a reduction in the pregnancy rate was observed.

THERAPEUTIC INDICATIONS – Adults and Children

Mebendazole (Antiox®) 50 mg/mL is indicated for the mass treatment of single or mixed gastrointestinal infestations by *Enterobius vermicularis* (pinworm); *Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm); *Ancylostoma duodenale*, *Necator americanus* (hookworm).

In patients living in heavily endemic areas, regular treatment with Mebendazole (Antiox®) 50 mg/mL (1-2 times a year) will substantially reduce the overall wormload and keep it well below the level of clinical significance.

CONTRAINDICATIONS

Mebendazole (Antiox®) is contraindicated in children below the age of 1 year for the mass treatment of single or mixed gastrointestinal infestations. In addition, Mebendazole (Antiox®) is contraindicated in persons with a known hypersensitivity to the drug or its excipients.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Convulsions in children, including in infants below one year of age, have been reported very rarely during postmarketing experience with Mebendazole (Antiox®) (see **Undesirable Effects**).

Mebendazole (Antiox®) has not been extensively studied in children below the age of 2 years. Therefore, Mebendazole (Antiox®) should be used in children aged 1-2 years only if the potential benefit justifies the potential risk (e.g. if their worm infestation interferes significantly with their nutritional status and physical development).

To reduce the risk of choking, Mebendazole (Antiox®) oral suspension should be considered for patients such as young children who are unable to swallow the tablet.

There have been rare reports of reversible liver function disturbances, hepatitis, and neutropenia described in patients who were treated with mebendazole at standard dosages for indicated conditions (see **Undesirable Effects – Postmarketing data**). These events, along with glomerulonephritis and agranulocytosis, have also been reported with dosages substantially above those recommended and with treatment for prolonged periods of time.

Results from a case-control study investigating an outbreak of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) suggested a possible relationship between SJS/TEN and the concomitant use of mebendazole and metronidazole. Further data suggesting such a drug-drug interaction are not available. Therefore, concomitant use of mebendazole and metronidazole should be avoided.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Concomitant treatment with cimetidine may inhibit the metabolism of mebendazole in the liver, resulting in increased plasma concentrations of the drug especially during prolonged treatment.

Concomitant use of mebendazole and metronidazole should be avoided (see **Special Warnings and Special Precautions for Use**).

PREGNANCY, BREAST-FEEDING AND FERTILITY

Pregnancy

Mebendazole has shown embryotoxic and teratogenic activity in rats and in mice. No harmful effects on reproduction were noted in other animal species tested (see **Non-Clinical Information**).

The possible risks associated with prescribing Mebendazole (Antiox®) 50 mg/mL during pregnancy, particularly during the first trimester, should be weighed against the expected therapeutic benefits.



Breast-feeding

Limited data from case reports demonstrate that a small amount of mebendazole is present in human milk following oral administration. Therefore, caution should be exercised when Mebendazole (Antiox®) 50 mg/mL is administered to breast-feeding women.

Fertility

Results of mebendazole reproduction studies showed no effects on fertility up to and including doses of 10 mg/kg/day (60 mg/m²) (see **Non-Clinical Information**).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Mebendazole (Antiox®) 50 mg/mL does not affect the mental alertness or driving ability.

DOSAGE AND METHOD OF ADMINISTRATION

Dosage

Enterobiasis, Ascariasis, Trichuriasis, hookworm and mixed infestations

1 dose of Mebendazole (Antiox®) 50 mg/mL suspension.

Special populations

Pediatrics

Enterobiasis, Ascariasis, Trichuriasis, hookworm and mixed infestations

Mebendazole (Antiox®) 50 mg/mL given as a single dose.

Pediatrics < 2 years of age

Because of the risk of convulsions, Mebendazole (Antiox®) is contraindicated in children below the age of 1 year for the mass treatment of single or mixed gastrointestinal infestations (see **Contraindications, Special Warnings and Special Precautions for Use**).

Mebendazole (Antiox®) has not been extensively studied in children below the age of 2 years. Therefore, Mebendazole (Antiox®) should be used in children aged 1-2 years only if the potential benefit justifies the potential risk (see **Special Warnings and Special Precautions for Use**).

Administration

No special procedures, such as diet or use of laxatives, are required.

UNDESIRABLE EFFECTS

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of mebendazole based on the comprehensive assessment of the available adverse event information. A causal relationship with mebendazole cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

The safety of Mebendazole (Antiox®) was evaluated in 6276 subjects who participated in 39 clinical trials for treatment of single or mixed parasitic infestations of the gastrointestinal tract. In these 39 clinical trials, no adverse reactions occurred in ≥1% of Mebendazole (Antiox®)-treated subjects. Adverse reactions occurring in <1% of Mebendazole (Antiox®)-treated subjects are shown in Table 1.

Table 1: Adverse Reactions Reported by <1% of Mebendazole (Antiox®)-Treated Subjects in 39 Clinical Trials

System/Organ Class

Adverse Reaction

Gastrointestinal Disorders

Abdominal Discomfort

Diarrhea

Flatulence

Skin and Subcutaneous Tissue Disorders

Rash

Postmarketing data

Adverse reactions first identified during postmarketing experience with Mebendazole (Antiox®) are included in Table 2. In the table the frequency categories are provided according to the following convention:

Very common ≥ 1/10

Common ≥ 1/100 and < 1/10

Uncommon ≥ 1/1000 and < 1/100

Rare ≥ 1/10000 and < 1/1000

Very rare < 1/10000, including isolated reports.

In Table 2, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 2: Adverse Reactions Identified During Postmarketing Experience with Mebendazole (Antiox®) by Frequency Category Estimated from Spontaneous Reporting Rates

System Organ Class

Frequency Category

Adverse Reaction

Blood and Lymphatic System Disorders

Very Rare

Agranulocytosis*, Neutropenia

Immune System Disorders

Very Rare

Hypersensitivity including anaphylactic reaction and anaphylactoid reaction

Nervous System Disorders

Very Rare

Convulsions, Dizziness

Gastrointestinal Disorders

Very Rare

Abdominal pain, Nausea, Vomiting

Hepatobiliary Disorders

Very Rare

Hepatitis, Abnormal liver function tests

Skin and Subcutaneous Tissue Disorders

Very Rare

Toxic epidermal necrolysis, Stevens-Johnson syndrome, Exanthema, Angioedema, Urticaria, Alopecia

Renal and Urinary Disorders

Very rare

Glomerulonephritis*

* Observed in higher and prolonged doses

OVERDOSE

In patients treated at dosages substantially higher than recommended or for prolonged periods of time, the following adverse reactions have been reported rarely: alopecia, reversible liver function disturbances, hepatitis, agranulocytosis, neutropenia, and glomerulonephritis. With the exception of agranulocytosis and glomerulonephritis, these also have been reported in patients who were treated with mebendazole at standard dosages (see **Undesirable Effects – Postmarketing data**).

Signs and symptoms

In the event of accidental overdose, abdominal cramps, nausea, vomiting and diarrhea may occur.

Treatment

There is no specific antidote. Activated charcoal may be given if considered appropriate.

STORAGE CONDITION

Store at temperatures not exceeding 30°C.

Keep out of reach of children.

AVAILABILITY

Amber bottle x 10 mL/Box of 1's

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